ADVANCES IN THE MANAGEMENT OF JUVENILE IDIOPATHIC ARTHRITIS

THE COMING OF AGE OF BIOLOGIC TREATMENT

JANNEKE ANINK

Advances in the Management of Juvenile Idiopathic Arthritis

The coming of age of biologic treatment

Colofon

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Advances in the Management of Juvenile Idiopathic Arthritis

The coming of age of biologic treatment

Stappen vooruit in de behandeling van juveniele idiopathische artritis
Het volgroeien van de behandeling met biologicals

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TABLE OF CONTENTS

Chapter 1. **Introduction, aim and outline**

THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS IN THE PRE-BIOLOGIC ERA

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic diseases, characterised by the presence of arthritis starting before the age of 16, persisting for over six weeks. According to the classification of the International League of Associations for Rheumatology (ILAR), seven different categories of JIA are defined based on clinical and laboratory findings and are described in table 1, together with their distribution (percentages are taken from several studies).[1 2]

Table 1 Description and incidence of JIA categories

JIA category	Characteristics	% of total JIA
Systemic JIA	Arthritis and daily fever ≥ 3 days, accompanied by at least one of the following: evanescent (non-fixed) erythematous rash, generalised lymph node enlargement, hepatomegaly/ splenomegaly, serositis	4-17
Oligoarticular JIA: Persistent form Extended form	Arthritis in 1-4 joints during the first 6 months of the disease Arthritis in 1-4 joints throughout the disease course Arthritis in > 4 joints after the first 6 months of the disease	27-60
Polyarticular JIA RF +	Arthritis in > 4 joints during the first 6 months of the disease, two or more positive tests for rheumatoid factor at least 3 months apart	2-7
Polyarticular JIA RF -	Arthritis in > 4 joints during the first 6 months of the disease, negative tests for rheumatoid factor	11-30
Psoriatic JIA	Arthritis and psoriasis, or arthritis and at least two of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first degree relative	2-11
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain, HLA-B27 antigen positive, onset in a boy >6 years old, acute anterior uveitis, HLA-B27 associated disease* in first degree relative	1-11
Undifferentiated JIA	Arthritis that does not fulfil criteria in one of the categories or meets criteria for more than one category	11-21

*Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute uveitis

JIA=juvenile idiopathic arthritis, RF=rheumatoid factor

Just as the disease, the prognosis is very heterogeneous. Some of the categories (predominantly the oligoarticular persistent form) have a very favourable prognosis. However the arthritis frequently continues into adulthood, particularly in the polyarticular categories.[3] The persistent disease activity, together with the extra-articular manifestations of the disease can lead to chronic functional disability, social and psychological impairments and a decrease of quality of life.[4-6]

No cure is available for JIA. Its treatment is therefore aimed at relieving the symptoms and if possible suppressing the disease activity, thereby preventing growth impairments, long term disability and a reduced quality of life. Especially for JIA patients with polyarticular or systemic forms of JIA, these goals were hard to reach. However, in the last three decades, the treatment of JIA has greatly progressed.

The first description of JIA appeared in medical literature in 1864.[7] Initially the disease was predominantly treated with basic supportive measures such as rest, physical therapy, support in the form of splints and relief in the form of hot baths or packs of paraffin. First line drug therapy existed of “rapidly acting” therapy in the form of aspirin, if necessary supplemented with corticosteroids, either oral or intra-articular. Second line, “slow-acting” therapy consisted of crysotherapy (intramuscular gold) and antimalarial agents or D-penicillamine.[8] In the early 1980s other non-steroidal anti-inflammatory drugs (NSAIDs) were approved for JIA and replaced aspirin as the first choice of treatment.[9] During the 1980s synthetic disease modifying anti-rheumatic drugs (DMARDs), which had been tested more extensively in adults with rheumatoid arthritis (RA), slowly came into use for JIA.[10] Two of these DMARDs, methotrexate and sulfasalazine, were both tested in randomized controlled trials (RCTs) and are currently part of the treatment of JIA.[11 12] Of the early slow-acting anti-rheumatic drugs (gold, D-penicillamine and antimalarians) the efficacy could not be demonstrated and these are now rarely used.[13 14] Methotrexate is effective to some extent in practically all patients, although still only 10-45% achieve a remission within one year of treatment.[11 15 16] At present, methotrexate is the recommended second-line drug after failure of NSAIDs and intra-articular corticosteroid injections.[17] All the drugs mentioned were unspecific with regard to their working mechanism. They were used in the treatment of JIA because of their apparent anti-inflammatory or immunosuppressive effects; however they did not affect the disease via a clearly understood mechanism of action.

BIOLOGIC TREATMENT OF JIA

This changed at the end of the 20th century. As a result of the increasing understanding of the inflammatory pathway, drugs were developed targeting specific components of this pathway. Because these new drugs are produced using recombinant DNA in living cells and are composed of natural products such as proteins, they are known collectively as biologicals or biologic agents.

The first biologic agents were inhibitors of tumour necrosis factor-alpha (TNF). TNF is an important cytokine that is predominantly produced by macrophages. It is generally thought of as a pro-inflammatory cytokine, which at low concentrations increases host defence mechanisms in tissues. Increased expression of TNF however results in excess inflammation and tissue damage. This is also the role TNF is thought to have in JIA as a result of innate and adaptive immune responses. It is placed at the head of an inflammatory cascade, itself mediating a variety of pathogenic effects and inducing the production of other pro-inflammatory cytokines. This results in synovial proliferation, recruitment and activation of inflammatory cells, neoangiogenesis and joint destruction.[18]

Etanercept, a TNF-receptor Fc-fusion protein that binds TNF, was the first biologic agent to be approved by the Food and Drugs Administration (FDA) and European Medicines Agency (EMA) for the treatment of JIA in 1999/2000. This followed an RCT that proved its short-term efficacy and safety in JIA patients.[19] Since then, an increasing number of biologic agents have been developed.

Growing understanding of pathophysiology of JIA led to the recognition of the systemic form of JIA as an auto-inflammatory rather than an auto-immune disease, requiring a different approach targeting different cytokines.[20] Instead of TNF-alpha which was the major cytokine targeted by the first biologic agents, IL-1 became a target for the treatment of systemic JIA. The biologic agents that are currently being used or tested for the treatment of JIA are listed in table 2.

Table 2 Biologic agents currently used or under investigation for JIA

Target	Biologic agent	Structure	Indication	FDA/EMA approval
TNF alpha	Etanercept	Receptor Fc-fusion protein	pJIA, ERA, psJIA	1999/2000 (approval for ERA and psJIA in 2012)
	Infliximab	Chimeric mAb	pJIA, ERA, psJIA	Not approved
	Adalimumab	Human mAb	pJIA	2008
	Golimumab	Human mAb	pJIA-trial	Not approved
	Certolizumab-pegol	Pegylated human mAb	pJIA-trial	Not approved
IL-1	Anakinra	Receptor antagonist	sJIA	Not approved
	Canakinumab	Human mAb	sJIA	Not approved
	Rilonacept	Receptor Fc-fusion protein	sJIA	Not approved
IL-6	Tocilizumab	Human mAb	sJIA, pJIA	2011 (2013 for pJIA)
CD80/86 (T-cell co-stimulation)	Abatacept	Receptor Fc-fusion protein	pJIA	2009, only after failure of TNF-inhibition
CD20 (B-cell)	Rituximab	Chimeric mAb	RF+ pJIA (rarely used)	Not approved
JAK	Tofacitinib	Small molecular inhibitor	pJIA-trial	Not approved

TNF=tumour necrosis factor, JIA=juvenile idiopathic arthritis, pJIA=polyarticular course JIA, ERA=enthesitis related arthritis, psJIA=psoriatic JIA, mAb=monoclonal antibody, sJIA=systemic JIA, IL=interleukin, RF+=rheumatoid factor positive, JAK=Janus kinase

STUDYING A NEW DRUG: THE ARTHRITIS AND BIOLOGICALS IN CHILDREN REGISTER

Aims and objectives

Proof of efficacy in an RCT is often mandatory for approval of a new drug by FDA and EMA. RCTs are characterized by strong control: a standardized treatment is uniformly provided within a standardized context to specified subjects who adhere completely to the treatment as delivered. Because of this strict standardization, each effect is assumed to be the direct result of the intervention being studied.[21] However, proven efficacy in an RCT does not directly imply effectiveness in real-world patients. The circumstances under

which RCTs are performed are not reflective of what happens in daily practice. Because the patients in RCTs are included according to very strict inclusion criteria, they may not reflect the real world JIA-population. The number of patients included is often too small to comment on predictive factors for response. Also, the time patients are followed is often too brief to conclude long term effects, delayed adverse events and the costs real world treatment will imply. Prospective observational studies are crucial to evaluate these factors in a non-selected patient population. Additionally these studies reflect decision-making in daily clinical practice and provide information on the effectiveness of drugs that are used off-label.

When etanercept was first marketed in the Netherlands and it was expected that other biologic agents would soon follow, this was the rationale behind the constitution of the Arthritis and Biologicals in Children (ABC) register.

Study design of the ABC register

The ABC register was founded in 2003 with the primary goal of determining the long-term effectiveness and safety of biologic therapies in JIA. It contains data prospectively collected from the introduction of etanercept in 1999 until data collection has stopped in 2014. It was a multicentre prospective observational study and aimed to include all JIA patients starting biologic treatment in the Netherlands. At first, it focused on including patients starting TNF-inhibitors, however because of the rapid development of other biologic treatments, the register widened its scope to include all biologic agents. Data was collected on paper, until in 2008, when the register became web-based to facilitate easy use for participating investigators and to guarantee accuracy and up-to-date information.[22] Ethical approval for the ABC register was granted by the Medical Ethics Committee at the Erasmus MC in Rotterdam and all other participating hospitals. Since the initial approval, ten amendments were made to the study protocol including radiological and bone mineral density evaluation and long-term follow-up of quality of life and disability.

In 2014 approximately 500 patients were registered. More than 3000 follow-up moments have been entered and the total follow-up duration of included patients has exceeded 1500 patient-years. Etanercept was the most frequently prescribed first biologic agent, but adalimumab and anakinra were increasingly prescribed during the course of the register.

Data collection in the ABC register

Upon inclusion in the ABC register, patient and disease characteristics were recorded. These included gender, date of birth, date of JIA onset, JIA category, laboratory findings,

medical history and previously used medication. Data was entered at the start of each biologic agent, and after three, six months and 15 months of treatment, and yearly thereafter, until the patient was transferred to adult care. In addition to these follow-up moments, data was entered at the time of any important events including when biologics were discontinued, the patient switched to a different type of biologic agent or when there were safety concerns.
At all of these follow-up moments, medication use and disease activity were recorded. The disease activity was recorded using the following variables:

1. Physicians' global assessment of disease activity on a visual analogue scale (VAS) (range 0-100mm, 0 best score)
2. Childhood Health Assessment Questionnaire (CHAQ) by patient/parent (range 0-3, 0 best score)
3. Global assessment of pain by patient/parent on a VAS (range 0-100mm, 0 best score)
4. Global assessment of wellbeing by patient/parent on a VAS (range 0-100mm, 0 best score)
5. Number of joints with active arthritis
6. Number of joints with limited range of motion
7. Erythrocyte sedimentation rate (ESR, mm/hour)

Using these disease activity variables, the Juvenile Arthritis Disease Activity Score (JADAS-10) could be calculated. JADAS-10 ranges from 0-40 and is calculated as the sum of four of the variables taken from the JIA core set: the scores of the physician and parent/patient global assessment (VAS 0-10), the reduced 10-active joint count and a normalized value of ESR to a 0-10 scale.[23]

Previous lessons from the ABC register

Two previous theses presenting results of the ABC register have been published. Firstly, the development of the web-based register itself was investigated.[22]
Most of the research performed in the ABC register focused on etanercept, because the majority of patients included in the register was treated with this biologic agent. Etanercept proved to be safe and effective, not only in suppressing disease activity, but also in improving quality of life and diminishing disability.[24 25] Cost-effectiveness was studied and although costs were substantial, the large gain in utility was deemed more important.[26]
In addition to the investigation of etanercept in the total – very heterogeneous – group of JIA patients included in the register, case studies were published on the effectiveness

of etanercept in the specific JIA categories psoriatic JIA and enthesitis related arthritis. Etanercept proved to be effective in both groups.[27 28]
The investigators looked deeper into the response to etanercept. Some patients were found to have a delayed response when treatment was continued after response criteria were not met after three months of treatment. Clinical factors associated with the response to etanercept were identified and dosing regimens were explored.[29-31]
At first only the response to etanercept was of interest, however, when patients appeared to be very responsive, and clinically inactive disease was achieved by a large part of patients, the possibility of discontinuing medication after successful treatment was investigated. The small study conducted in the ABC register indicated that at least half of patients discontinuing etanercept flared within a year.[32] Serum levels of MRP8/14, a potential biomarker associated with disease activity, were able to predict a flare after discontinuation of etanercept in patients with systemic JIA.[33]

OBJECTIVE AND OUTLINE THESIS

The objective of the ABC register is thus to evaluate the long-term effectiveness and safety of biologic agents and to observe the prescription patterns of these agents in daily clinical practice. This thesis will build on the previous results of the ABC register by investigating not only the effectiveness of etanercept, but other biologic agents as well. In addition it explores possibilities for improving care of JIA patients by looking at various new methods for monitoring JIA patients during their treatment.
Chapter 2 extends the investigation of the efficacy of TNF-inhibitors. In **chapter 2.1** the effectiveness of TNF-inhibitors is studied in patients with the oligoarticular JIA category, who are normally not eligible for treatment with this agent. In **chapter 2.2** we investigate whether the previously shown improvement in quality of life and functional outcome is sustained more than 5 years after start of etanercept.
Because an increasing number of biologic agents have become available for the treatment of JIA, **chapter 3** is focused on these newly available drugs and the changes in prescription patterns due to these drugs in daily practice. In **chapter 3.1** these prescription patterns are studied in more detail by describing the general trends in biologic treatment in the ABC register, while the decisions paediatric rheumatologists make when they have to choose between two TNF-inhibitors are the subject of **chapter 3.2**. In **chapter 3.3** comparative efficacy of the available biologic agents is investigated in an indirect comparison of the clinical trials and in **chapter 3.4** switches in biologic treatment after failure of etanercept

and their effectiveness are studied. In **chapter 3.5** the possibilities of comparing different biologic agents are examined and the difficulties that can be encountered in doing so discussed.

Chapter 4 deals with new developments in the monitoring of JIA. In **chapter 4.1** a patient reported joint count is investigated and in **chapter 4.2** and **chapter 4.3** the feasibility and reliability of a new automated method for determining bone age and bone health are explored**.** In chapter 4 also biomarkers are studied, such as the previously mentioned MRP8/14 (now in non-systemic JIA, **chapter 4.4**) and anti-carbamylated proteins (anti-CarP, **chapter 4.5**).

In **chapter 5** the conclusions of this thesis are discussed in light of current practice, methodological considerations, and implications for future research.

Finally, **chapter 6** is a summary of the complete thesis.

Chapter 2. **Effectiveness of the first available biologic treatment: TNF-inhibitors**

Chapter 2.1 **TNF-inhibitors in persistent oligoarticular JIA**

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ABSTRACT

Objective. Because TNF inhibitors are not approved for persistent oligoarticular JIA (oJIA), although they are used off-label, we evaluated their effectiveness in patients in this category.

Methods. Persistent oJIA patients were selected from the Dutch Arthritis and Biologicals in Children (ABC) register, an ongoing multicentre prospective study that aims to include all Dutch children with JIA using biologic agents. Response was assessed by the JIA core-set disease activity variables and modified Wallace criteria for inactive disease.

Results. Until February 2011, 16 persistent oJIA patients (68.8% females) had been included in the register. Median age of onset was 8.4 years [interquartile range (IQR) 2.1–13.5 years]; history of uveitis in 18.8%; ANA-positive 56.3%. All had previously used MTX, and 81.3% had used IA CSs. Median follow-up after the introduction of biologic treatment was 13.7 months (IQR 8.3–16.7 months). Fourteen patients started etanercept and two patients who had active arthritis as well as uveitis started adalimumab. Although patients with persistent oJIA had few affected joints [median of two active joints at the start of biologic (IQR 1–3)], the patient/parent assessments of pain [median visual analogue score (VAS) 51 (IQR 1–64)] and well-being [median VAS 44 (IQR 6–66)] were high. Additionally, their physician evaluated the disease activity as moderately high [median VAS 36 (IQR 4–65)]. After 3 months this decreased to 0 (IQR 0–30) and 63% achieved inactive disease. After 15 months the disease was inactive in 9/10 observed patients. TNF inhibitors were tolerated well.

Conclusion. TNF blocking agents seem an effective and justifiable option in persistent oJIA when treatment with IA CS injections and MTX has failed.

INTRODUCTION

The International League of Associations for Rheumatology (ILAR) distinguishes oligoarticular JIA (oJIA) as one of the seven categories of JIA,[1] defining it as arthritis affecting four or fewer joints during the first 6 months of disease. Based on the number of joints affected thereafter, oJIA is subdivided into the persistent form (four or fewer joints) and the extended form (over four joints).

Persistent oJIA is a well-defined subset. Typically, it starts before the age of 6 years, and affects girls more often than boys. Patients have asymmetric arthritis, predominantly in knees and ankles. They have a high risk of chronic anterior uveitis (up to 30%), and ANAs are often present (70–80%).[34]

For many years, persistent oJIA was treated with NSAIDs and IA CS injections. In recent years a more aggressive treatment regimen has been adopted, including synthetic DMARDs, such as MTX, in order to achieve inactive disease. However, additional treatment with DMARDs does not lead to inactive disease in all patients. Figures on long-term outcome vary greatly between cohort studies.[35-38] Although persistent oJIA patients are thought to have the best outcome, a recent comprehensive cohort study reports 15% of patients to have joint destruction and/or visual impairment in the long term.[3]

For patients at risk, the ACR now recommends adding TNF-α-blocking agents.[17]

The TNF-α-receptor blocking agent etanercept has proved to be effective in polyarticular JIA.[39] [40] However, persistent oJIA patients have always been excluded from clinical trials. Since 2000 etanercept is registered worldwide only for refractory JIA patients with a polyarticular course. In 2008, adalimumab was registered for the same indication.[41] This monoclonal antibody against TNF-α is also used effectively for treatment of JIA-associated uveitis.[42]

As more experience is gained, TNF-α blockers are also prescribed off-label for refractory persistent oJIA. However, no detailed studies have focused on their effectiveness in this category. The present study evaluates the effectiveness of TNF-blocking agents in all Dutch persistent oJIA patients included in the Arthritis and Biologicals in Children (ABC) register. Additionally, we compared persistent oJIA patients with other patients in the register.

METHODS

Data were retrieved from the ABC register, an ongoing multicentre prospective observational register that aims to include all Dutch JIA patients treated with biologic agents since 1999 to monitor effectiveness and safety.[22] In the ABC register, patient characteristics were retrieved

at start and data on disease activity variables at start, at 3 months and yearly thereafter. All patients were seen regularly by their treating physician. Data were also entered at time of important events, including discontinuation or switch of biologic agents. Adverse events (AEs) and serious AEs (SAEs) were reported on a continuous basis.[22 43] Flaring of arthritis or uveitis was regarded as a measure of treatment response. This study is embedded in the ABC register; no additional approval was needed to perform the study.

We selected patients fulfilling the ILAR criteria for persistent oJIA,[1] included in the ABC register from its foundation to February 2011. Patients without active arthritis starting biologic treatment for uveitis were not included. Patient records of persistent oJIA patients were retrospectively checked for consistency and disease flares. Of the baseline data 12.5% and of the follow-up data 14% on disease activity variables were missing {median 0 variables missing/patient [interquartile range (IQR) 0–3]}.

We compared baseline characteristics of persistent oJIA patients with those of other JIA patients included in our register. In this analysis, we excluded patients with systemic JIA (n=68). We divided the non-systemic JIA patients in two groups: patients with four or fewer active joints and patients with over four active joints at start of biologic treatment.

The response to treatment was assessed with variables of the JIA core set according to an intention-to-treat analysis.[44] A modified definition of inactive disease was used: no active arthritis, no uveitis, normal ESR (values under 20 mm/h) and a physician's global assessment of disease activity <10 mm indicating no disease activity.[45] This last cut-off was chosen because we experience that physicians are reluctant to set disease activity at zero, as the disease is not cured and patients still require medication. Descriptive statistics were reported as absolute frequencies or as medians with IQR. Fisher's exact, Kruskal–Wallis and Mann–Whitney U-tests were used to perform comparisons as applicable. A $P < 0.05$ was considered statistically significant. SPSS version 17.0.1 was used for all analyses.

RESULTS

Of the 408 patients included in the register until February 2011, 16 patients had persistent oJIA (3.9%). Patient and disease characteristics of patients with persistent oJIA and patients with other non-systemic JIA categories in the register are shown in table 1. Patients with other non-systemic JIA categories had higher disease activity and were treated more extensively than persistent oJIA patients. Persistent oJIA patients differed from the non-systemic patients with over four active joints at start, especially with regard to uveitis and ANA positivity. They resembled the patients with non-systemic JIA categories

with four or fewer active joints at initiation of biologic therapy on most characteristics, extended oJIA being the most common JIA category in this group.

Table 1 Patient and disease characteristics

Characteristic	Persistent oJIA (n=16)	Non-systemic JIA categories other than persistent oJIA	
		Four or fewer active joints at start of biologic (n=69)	Over four active joints at start of biologic (n=258)
Female, n (%)	11 (68.8)	44 (63.8)	185 (71.7)
Median age at onset (IQR), years	8.4 (2.1–13.5)	6.8 (2.8–10.6)	8.3 (3.5–11.5)
Median age at start of first biologic (IQR), years	12.1 (8.5–16.1)	13.4 (9.4–15.5)	12.5 (9.2–15.2)
Median JIA disease duration before start of biologic (IQR), years	2.0 (1.2–6.0)	4.1 (1.8–7.9)	2.7 (1.3–5.7)
History of uveitis, n (%)	3 (18.8)	10 (14.5)	12 (4.7)**
ANA positivity, n (%)	9 (56.3)	33 (47.8)	67 (26.0)*
HLA-B27 positivity, n (%)	2 (12.5)	10 (14.5)	16 (6.2)
RF positivity, n (%)	–	6 (8.7)	30 (11.6)
Category JIA, n (%)			
Polyarticular RF negative	–	18 (26.1)	136 (52.7)
Polyarticular RF positive	–	8 (11.6)	29 (11.2)
Oligoarticular persistent	16 (100)	–	–
Oligoarticular extended	–	27 (39.1)	58 (22.5)
PsJIA	–	7 (10.1)	19 (7.4)
Enthesitis-related arthritis	–	9 (13.0)	16 (6.2)
First-introduced biologic, n (%)			
Etanercept	14 (87.5)	61 (88.4)	252 (97.7)
Adalimumab	2 (12.5)	7 (10.1)	4 (1.6)
Infliximab	–	1 (1.4)	2 (0.8)
Previously used medications, n (%)			
NSAID	15 (93.8)	68 (98.6)	250 (96.9)
Systemic CSs	3 (18.8)	26 (37.7)	108 (41.9)*
IA CSs	13 (81.3)	36 (52.2)*	59 (22.9)**
MTX	16 (100.0)	68 (98.6)	238 (92.2)
Other DMARDs besides MTX	2 (12.5)	9 (13.0)	52 (20.2)

Co-medication at start of biologic, n (%)			
NSAID	7 (43.8)	46 (66.7)**	217 (84.1)**
Systemic CSs	–	8 (11.6)	70 (27.1)*
IA CSs	3 (18.8)	7 (10.1)	7 (2.7)*
MTX	10 (62.5)	50 (72.5)	231 (89.5)**
DMARD other than MTX	1 (6.3)	6 (8.7)	13 (5.0)
Median disease activity parameters of patients with active arthritis at baseline (IQR)			
VAS physician	36 (24–51)	40 (30–60)	60 (45–73)**
Total CHAQ score	0.30 (0.00–0.75)	0.88 (0.27–1.40)*	1.50 (1.00–2.00)**
VAS pain	51 (1–64)	41 (12–65)	60 (30–77)*
VAS well-being	44 (6–66)	48 (13–64)	54 (31–75)
Number of active joints	2 (1–3)	3 (2–4)*	10 (6–16)**
Number of limited joints	1 (1–2)	2 (1–4)*	6 (4–12)**
ESR	10 (4–20)	13 (7–28)	15 (7–32)

*$P \leq 0.05$, **$P \leq 0.001$, persistent oJIA patients compared with the two groups of other non-systemic JIA patients. CHAQ=Childhood HAQ.

Most persistent oJIA patients (*n*=14) started TNF inhibitors because of persistent arthritis, all started etanercept. The two patients starting adalimumab had active arthritis as well as uveitis. Median follow-up after introduction of a TNF inhibitor was 13.7 months (IQR 8.3–16.7 months). All patients were previously treated with MTX; nine up to a maximum dose of ≥15 mg/m^2 for >6 months, the other seven patients did not reach the maximum dose due to intolerance. Of these seven patients three received MTX for <6 months. Three patients were not treated with IA CSs, because of a disease course dominated by severe refractory uveitis and/or arthritis in joints less accessible for injections. The other 13 patients were treated with one or multiple injections (range 2–5 injections/joint). In most patients knees were involved (a total of 22 knees). Other affected joints were ankles (nine), elbows (three), fingers (three), hip (two), shoulder (one) and TM joint (one). Eleven patients had conventional radiographs taken of the affected joints. Two patients had erosive deformities of the ankle. Two other patients had growth disturbances of the knees.

Effectiveness

Table 2 shows the response to treatment in persistent oJIA patients. All disease activity variables decreased within 3 months. An even greater decrease could be seen after 15

months of follow-up. Inactive disease was reached by 10 patients (63%) within 3 months. Seven of these patients had an observed follow-up of 15 months and had by then achieved remission on medication. At 15 months, in total 9 out of 10 observed patients had achieved inactive disease.

Table 2 Change of disease activity variables

Disease activity variables	Start (n=16)	3 Months (n=16)		15 Months (n=10)	
	Median (range)	Median (range)	No. normalized/ no. observed	Median (range)	No. normalized/ no. observed
VAS physician	36 (4–65)	2 (0–13)	10/12	0 (0–30)	9/10
Total CHAQ score	0.3 (0.0–0.9)	0.1 (0.0–1.0)	6/13	0.1 (0.0–0.6)	3/6
VAS pain	51 (0–71)	6 (0–75)	3/13	0 (0–34)	4/7
VAS well-being	44 (0–74)	5 (0–75)	5/13	0 (0–20)	5/7
Number of active joints	2 (1–4)	0 (0–1)	13/16	0 (0–2)	9/10
Number of limited joints	1 (0–3)	0 (0–2)	8/14	0 (0–2)	8/10
ESR	10 (2–60)	3 (2–30)	11/15	3 (2–29)	9/10
Patients with inactive disease, %	NA	NA	10/16	NA	9/10

All variables presented as median (range). Definition of normalized: VAS physician <10; total CHAQ score=0; VAS pain=0; VAS well-being=0; number of active joints=0; number of limited joints=0; ESR <20 mm/h; CHAQ=Childhood HAQ; NA=not applicable.

The majority of patients continued concomitant MTX. Most patients (*n*=13) were not treated with IA CSs during anti-TNF treatment. Three patients received IA CSs simultaneously with the start of etanercept. These patients had been treated with IA CSs in several joints before, with insufficient response (lasting <5 months). All three patients achieved inactive disease within 3 months, which was sustained for the observed follow-up of 14 months in one patient. The other two patients had a disease flare after 10 months. One patient switched from etanercept to adalimumab and achieved inactive disease thereafter.
Two of 16 persistent oJIA patients discontinued TNF inhibitor because of disease remission after 10 months. One of these patients showed lasting remission during the observed follow-up (4 months); the other patient flared within 1 month. The other 14 patients continued using TNF inhibitor.

Safety

A total of 18.2 patient-years after introduction of TNF inhibitor (16.0 patient-years on etanercept and 2.2 patient-years on adalimumab) were observed. Two SAEs were reported during etanercept use (restrictive pulmonary function and perforated appendicitis). No AEs were reported during adalimumab use. No permanent discontinuation due to AEs occurred.

DISCUSSION

This is the first study that extensively evaluates the effectiveness of TNF blocking agents in persistent oJIA patients. Since most patients started etanercept, our results mainly reflect the effectiveness of etanercept.

After introduction of a TNF blocking agent, disease activity rapidly declined. This result was maintained and even improved after 15 months, when almost all of the patients with available follow-up had achieved inactive disease. A decrease in disease activity was found in patients included in our register comparable to that in other (non-systemic) categories of JIA.[40] One recent observational study also reports on 38 persistent oJIA patients (5% of the total studied population) being treated with etanercept. Of these oJIA patients 53% achieved inactive disease (using the modified inactive disease criteria as defined in the present study) and 13% remission on medication.[46] No additional patient or disease characteristics are described and follow-up duration of persistent oJIA patients is not provided. These combined results provide support for treatment with TNF inhibitors in some persistent oJIA patients.

Despite the fact that biologic agents were not tested in persistent oJIA patients in clinical trials, and therefore not licensed for this JIA category, paediatric rheumatologists perceived the need to prescribe TNF blocking agents to a small number of persistent oJIA patients. One might argue that this is related to the higher prevalence of uveitis in this group; another indication for biologic treatment. However, only in two patients did the presence of refractory uveitis contribute to the decision to prescribe the TNF inhibitor.

The persistent oJIA patients in our study may represent a specific oJIA subset, requiring a different treatment approach. The onset age of our patients is higher (comparable to other non-systemic JIA patients) and the prevalence of ANA is lower than in persistent oJIA patients described in the literature.[34] The categorization of JIA is subject to ongoing debate; classifying JIA by other factors than number of joints at onset has been proposed.[47] [48] The recently published ACR recommendations for management of JIA use an alternative way of categorizing: treatment choice is not purely based on JIA category, but rather on

disease activity, prognostic features and response to previous therapy.[17] When applied to our study, only six patients were treated according to these recommendations. The 10 patients not fulfilling the criteria had ongoing relapsing arthritis despite use of IA CSs and DMARDs. Their scores for patient/parent assessments of pain and well-being were identical to other non-systemic JIA patients treated with TNF inhibitors. It seems that these recommendations are not fully applicable in daily practice.

A reason to be reticent with prescribing TNF inhibitors to persistent oJIA patients may be a safety concern. In this study, insufficient patient-years are observed to be able to evaluate the safety of TNF inhibitors. Although TNF blockers are observed to be well tolerated in previous reports on patients with all JIA categories,[40 49] there is still insufficient knowledge about the long-term effects. Balancing the risks and benefits remains important when considering treatment with TNF blockers.

The present study has some limitations: the small number of patients and the short follow-up duration. The 16 patients included in this study were the only persistent oJIA patients in the Netherlands initiating TNF blocking agents since its introduction. To our knowledge this is the largest case series to date reporting detailed information on persistent oJIA patients only.

We further chose not to use the ACR Pedi 30, 50, 70 response criteria, which in our opinion are more appropriate for polyarticular disease. They do not capture the full degree of change in disease activity when individual baseline variables are low, as is the case in persistent oJIA. Today no specific instrument evaluating oligoarticular patients is available; therefore, the response to treatment was evaluated by change on the single core-set disease activity variables and the composite score for inactive disease.

Three of our patients were treated with IA CSs at start of etanercept and subsequently achieved inactive disease within 3 months. This inevitably results in a biased evaluation of response to the newly introduced TNF inhibitor. However, this is inherent to the nature of the current study and reflects daily clinical practice.

In conclusion, the results suggest that TNF blockers are effective in persistent oJIA patients who were refractory to MTX treatment and IA CS injections. Persistent oJIA patients treated with TNF inhibitors resemble other non-systemic JIA patients from our register with regard to age at onset and certain measures of disease activity. In these more severely affected persistent oJIA patients treatment with TNF inhibitors is a justifiable option.

Chapter 2.2 **Long term quality of life and functional outcome of patients treated with etanercept: a longitudinal follow-up study**

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Submitted as:
Janneke Anink, Femke H.M. Prince, Maryanne Dijkstra, et al. Long-term quality of life and functional outcome of patients with juvenile idiopathic arthritis in the biologic era; a longitudinal follow-up study in the Dutch arthritis and biologicals in children register

ABSTRACT

Objectives. To longitudinally investigate functional outcome, health related quality of life (HRQoL) and treatment strategies in juvenile idiopathic arthritis (JIA) patients who started etanercept more than 5 years ago.

Methods. We approached patients whose HRQoL changes were described previously in a sub-analysis of the Dutch Arthritis and Biologicals in Children register. Recent disease status, comorbidities and structural damage were retrieved. Disability and HRQoL were assessed by (Child) Health Assessment Questionnaire ((C)HAQ), Child Health Questionnaire, Short Form 36 (SF-36) and Health Utilities Index Mark 3. Changes over time were analysed with linear mixed models.

Results. 43 patients (81% response) started etanercept median 8.5 years ago. Median age at time of long-term analysis was 22 (IQR: 18 to 24), 42% had a (C)HAQ of 0.00. HRQoL outcome was similar to HRQoL after start of etanercept, except for bodily pain, which deteriorated to baseline levels at start of etanercept. VAS pain also worsened, but less than bodily pain on the SF-36. Unemployment (12%) was comparable to the general population; educational level was higher. Use of biologic agents: 40% etanercept, 40% other biologic agents, and 20% none. Joint surgery occurred in 14% of patients.

Conclusions. The HRQoL improvement was sustained after 8.5 years. Disability scores were low. On daily life aspects, patients functioned comparable or better than their peers. Persistence and possible deterioration of radiologic damage stress the importance of early treatment. Chronic pain - even in inactive disease - remains an important issue, affecting patients' quality of life.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic disease, with many JIA patients having ongoing active disease into adulthood.[35 38 50-52] During the last decades, several long-term follow-up studies indicated that JIA causes chronic disability and impairments in social life, due to both articular and extra-articular manifestations of the disease.[4]
Most of these studies however, were performed in the 1990's, when biologic treatment was not yet available. With the introduction of biologic agents, short term outcomes improved significantly, specifically for JIA patients in whom the disease could not be controlled with conventional DMARDs.[40 46] Only one cross-sectional study has been published investigating the long-term outcomes of JIA patients starting biologic treatment (etanercept) as a child.[53] Patients in this study had less JIA related damage and disability and a better health related quality of life (HRQoL) compared to JIA patients from a historical cohort not treated with biologic agents.
In 2010, a sub-analysis of the Dutch Arthritis and Biologicals in Children (ABC) register longitudinally investigated disease activity and HRQoL of 53 patients from the start of etanercept onwards until 27 months after start.[24] Not only did the arthritis subside rapidly in a large proportion of these patients, HRQoL also improved substantially. For the present study we contacted these 53 patients, aiming to investigate whether: 1. the control of active disease with etanercept in these patients was persistent, 2. patients needed to be treated with other biologic agents, and 3. improvement in HRQoL was sustained. Functional outcome, structural damage and comorbidities were additional topics of interest.

METHODS

The ABC register

The ABC register is a multicentre prospective observational study. It aimed to include all Dutch JIA patients who initiated biologic agents. Patients were followed up until they transitioned to adult care. The register was founded in 2003 and contains prospectively collected data since 1999. The study protocol was approved by the Medical Ethics Committee at Erasmus MC Rotterdam and by all participating hospitals.[40]

Patient selection and additional data collection

53 patients whose HRQoL following etanercept treatment was studied previously were asked to participate.[24] All were included in the ABC register before 2007. At that time, 71

patients from the centres participating in this sub-analysis had been included in the ABC register. The 53 patients that participated in the previous study were not different from the 18 patients that did not participate with regard to patient and disease characteristics. Patients were contacted through their last known physician. Written consent was obtained according to the declaration of Helsinki. Contact details of 47 patients were retrieved. The other six patients were lost to follow-up (patient flow-chart in supplementary files).
Permission was asked to retrieve information on disease status, comorbidity, structural and radiological damage and medication from the patient's current physician. Structural damage was defined as persistent changes in joints or other organs resulting from disease activity or medication. Radiological damage was defined as any report of cartilage damage, joint space narrowing or erosive changes. Following the domains of the Juvenile Arthritis Damage Index for extra-articular damage (JADI-E), the following types of extra-articular damage were assessed: ocular, musculoskeletal non-articular, cutaneous, endocrine and secondary amyloidosis.[54]
Through questionnaires, patients were asked to provide information on marital status, housing, education and employment. Highest achieved education level in Dutch categories were recoded into International Standard Classification of Education 2011 levels (ISCED 2011).[55] A patient-reported joint count was used when the physician could not provide a recent report of the disease activity. This was the case in 6 patients.
In adult patients, disability and HRQoL were measured by Health assessment questionnaire (HAQ), the Medical Outcomes Short Form 36 (SF-36) and the Health Utility Index mark 3 (HUI3) self-assessment.[56-58] In patients younger than 17, the CHAQ, Child Health Questionnaire (CHQ, which is closely related to SF-36) and the proxy assessment of the HUI3 were used.[59-61] An extensive description of all questionnaires can be found in the supplementary files. For the purpose of the current study, only the identical domains and the two summary scores of CHQ and SF-36 were reported and combined for figures and analyses. The reference values of these concepts were nearly the same, and therefore a comparison with the normal population would not be affected.[57 61]
The scores on the preference based HUI3 result in single and multi-attribute utilities on a scale from 0 (dead) to 1 (perfect health).[62]
HRQoL measured in this long-term follow-up study was graphically compared to the patients' own reported HRQoL at start of treatment and at the last available follow-up measurement, as described in the prior study by our group.[24] In figures and tables, the latter was referred to as "the intermediate follow-up" in the present manuscript. Measurements of the intermediate follow-up were at a mean of 15 months for the CHQ, and at a mean of 27 months for HUI3 and CHAQ.

Treatment effectiveness measures

Response was defined as having achieved at least an ACRpedi50 response after 3 months of treatment. Non-response was defined as having achieved a response lower than ACRpedi50. The ACRpedi50 response implies that a patient has improved ≥50% on three of the JIA core set variables and has worsened ≤30% on no more than one variable.[44] The disease was said to be inactive when the physician stated the disease was inactive and/or there were no joints with active arthritis, ESR <20 mm/hr (if available) and the physician's global assessment was < 10 mm.[45] In cases where the physician did not provide a recent report of disease activity a patient's VAS < 10 mm was required for assignment of inactive disease, combined with 0 active joints on the patient-reported joint count.

Statistical analysis

Descriptive statistics were reported as absolute frequencies, median with interquartile range (IQR) or mean with standard deviation (SD). For evaluating change in HRQoL measures over time we used linear mixed models with time as fixed covariate, a random intercept, and variance components as covariance structure (the default). For this analysis all available follow-up moments were used. A P-value <0.05 was considered statistically significant. IBM SPSS Statistics for Windows, Version 21.0 (Armonk NY: IBM Corp.) was used for all analyses.

RESULTS

Patients

Of the 53 patients in the original study, 43 participated in the long-term follow-up (81% response, for flowchart see supplementary files). One patient filled out the questionnaires, but did not give permission to contact the current treating rheumatologist. The patients who did not participate did not differ substantially from those who did. The characteristics of all patients are shown in table 1. The majority of patients was still in rheumatologic care (n=41 (95%)) of which 31 patients (76%) had transferred to adult care.

Table 1 Patient and disease characteristics

Characteristic	Patients included in this study n=43	Patients lost to follow-up n=10
Female, n (%)	28 (65)	5 (50)
Age at onset JIA, median (IQR), yrs	8.2 (5.0-10.0)	5.5 (1.7-10.4)
Disease duration at start etanercept, median (IQR), yrs	3.1 (1.4-5.1)	2.6 (0.9-5.1)
Age at long-term follow-up, median (IQR), yrs	22.0 (17.9-24.5)	18.9 (15.4-22.7)
Age at long-term follow-up, categorized		
< 17 years of age, n (%)	8 (19)	3 (30)
> 17 years of age, n (%)	35 (81)	7 (70)
Time between start etanercept and long-term follow-up, median (IQR), yrs	8.5 (7.7-10.3)	10.0 (8.2-11.0)
JIA category, n (%)		
Systemic JIA	12 (28)	2 (20)
Polyarticular RF negative JIA	12 (28)	4 (40)
Polyarticular RF positive JIA	7 (16)	1 (10)
Oligoarticular Extended JIA	8 (19)	2 (20)
Psoriatic JIA	3 (7)	-
ERA	1 (2)	1 (10)
Disease activity at start etanercept		
JADAS-10,[23] median (IQR) (range 0-40)	23 (18-25)	21 (19-27)
CHAQ, median (IQR) (range 0-3)	1.85 (1.25-2.33)	2.00 (1.43-2.18)
Responders to etanercept after 3 months of treatment (≥ACRpedi50)	33 (77)	7 (70)
HRQoL (CHQ) at start etanercept		
MCS, median (IQR) (range 0-100)	48 (42-54)	37 (24-48)
PCS, median (IQR) (range 0-100)	27 (11-45)	13 (0-32)
Inactive disease at long term follow-up, n (%)	29 (67)	NA

JIA=juvenile idiopathic arthritis, ERA=enthesitis related arthritis, JADAS=juvenile arthritis disease activity score, CHAQ=childhood health assessment questionnaire, HRQoL=health related quality of life, CHQ=child health questionnaire, MCS=mental component summary score, PCS=physical component summary score

Etanercept treatment

Most patients (81%) discontinued etanercept at some point during their disease course. Reasons for stopping were unsatisfactory response (n=7), loss of response (n=4), adverse events (n=2), uveitis flare (n=1) and a pregnancy wish (n=2). However, the majority

discontinued etanercept because of inactive disease (n=18 (56%)). The disease flared in 14 of these patients (79%) within a median of 9 months (range: 1-69 months). The other 4 patients remained flare-free until last follow-up (10 to 78 months).

Other biological and synthetic DMARD treatment

During the disease course, 16 patients (38%) used other biologic agents. At last follow-up, 41% of patients were still or again using etanercept. One fifth of our patients (n=8) were not using any anti-rheumatic drug. The majority (n=6) of these patients were male, and 63% (n=5) had systemic JIA. Of the remaining 34 patients who were still treated, 3 only used synthetic DMARDs, 16 only used a biologic agent and 15 were treated with a combination of a synthetic DMARD and a biologic agent. Details on current and previous treatment are shown in table 2.

Table 2 Treatment characteristics

Treatment characteristics	N=42
Current DMARD treatment, n (%)	18 (43)
Methotrexate	14 (38)
Hydroxychloroquine	3 (8)
Leflunomide	1 (3)
Sulfasalazine	2 (5)
Mycophenolate mofetil	1 (3)
Current biologic treatment, n (%)	31 (74)
Etanercept	17 (40)
Adalimumab	5 (12)
Infliximab	4 (10)
Anakinra	2 (5)
Tocilizumab	2 (5)
Rituximab	1 (2)
None	11 (26)
Duration off biologic medication, median (range), months (n=11)	42 (3-78)
No current anti-rheumatic treatment, n (%)	8 (19)
Number of ever used biologic agents, median (range)	1 (1-5)
Ever used biologics other than etanercept, n (%)	17 (40)
Adalimumab	14 (33)
Infliximab	8 (19)

Anakinra	5 (12)
Abatacept	3 (7)
Tocilizumab	3 (7)
Rituximab	1 (2)

DMARD=disease modifying anti-rheumatic drug

Structural damage and comorbidity

Half of our patients reported structural damage (n=21) (table 3), most frequently articular damage (n=17). In 14 of the 17 patients with joint destruction, some form of radiological damage was already present before start of etanercept. The systemic and polyarticular RF positive subtypes more often had radiological damage than other subtypes. (p=0.002, Fisher's Exact test).

More than half of our patients (55%) reported one or more comorbidities (table 3). Most were diagnosed after the start of etanercept. There were no reports of demyelinating conditions or malignancies.

Table 3 Structural damage and comorbidity

Structural damage	**N=42**
Number of patients with structural damage, n (%)	21 (50)
Type of damage, n (%)	
Severe joint destruction, joint surgery needed	6 (14)
Joint destruction, no joint surgery needed (yet)	11 (26)
Residual joint abnormalities and contractures	5 (12)
Severe osteoporosis	2 (5)
Severe growth impairment (deviation of > 2SD)	3 (7)
Debilitating rheumatoid nodule	1
Scapular dyskinesia	1
Ruptured Baker's cyst	1
Comorbidity	
Patients with comorbidity, n (%)	23 (55)
Comorbidity (diagnosed before start of etanercept)	
Pyramidal syndrome	1
Epilepsy	1
Recurrent infections	1
Cardiac arrhythmia	1

Comorbidity (diagnosed after start of etanercept)	
Generalized problems	
Chronic pain syndrome/ fibromyalgia	3
Chronic stomach complaints (no IBD)	3
Serious/recurrent infections	7
Anaemia	1
Angioneurotic oedema (probably infectious)	1
Neurological	
Tension headache	2
Carpal tunnel syndrome	1
Epilepsy	1
Mental health problems	2
Cardiovascular/haematological	
Pericarditis	1
Pernicious anaemia	1
Auto-immune phenomena	
IBD	2
Psoriasis	1
Uveitis	2
Other	
Perthes	1
Angiofibroma	1

SD=standard deviation; IBD=inflammatory bowel disease

Quality of life - living arrangements, education and employment

Patients were relatively highly educated compared to the general population in the Netherlands in the age range of 15-25 years (table 4).[63] The percentage of patients without work was comparable to the unemployment rate for the general population in the age range of 15-25 years in 2013 (12% and 16% respectively), although a higher percentage receives some form of disability benefit.[63] Almost 50% of patients >17 years old (n=16) indicated they felt limited in their choice of work or education. Half of our patients participated in some form of sport, in which they exercised for an average of 3.7 hours per week.

Table 4 Living, education and employment

Living, education and employment	≤ 17 years (n=8)	≥ 18 years (n=35)
Living arrangements, n (%)		
With parents	8 (100)	23 (66)
Alone	-	2 (6)
With partner	-	7 (20)
With partner and child	-	1 (3)
With roommates	-	2 (6)
Adapted housing, n (%)	1 (13)	6 (17)
Type of adaptation		
Stair lift	1	2 (6)
Adapted bathroom	-	1 (3)
Ground floor bedroom, specially build	-	2 (6)
Adapted furniture	-	3 (9)
Highest achieved education ISCED 2011 level, n (%)		
Special needs	-	1 (3)
ISCED 1 (primary education)	7 (88)	1 (3)
ISCED 2 (lower secondary education)	1 (13)	6 (17)
ISCED 3/4 (upper secondary/ post-secondary non-tertiary)	-	19 (54)
ISCED 6/7* (bachelor/master)	-	8 (23)
Employment		
Paid employment part time	2 (25)	14 (40)
Paid employment full time	-	6 (17)
Student	-	19 (54)
Unemployed	-	2 (6)
Social security/ disability benefit	-	2 (6)

*ISCED level 5 not applicable

Quality of life - disease specific HRQoL

Disease-specific HRQoL was measured by CHAQ or HAQ, depending on the age of the patient. CHAQ scores (median 0-83, IQR: 0.33-0.97) at the long-term follow-up evaluation were higher than HAQ scores (median 0.00, IQR: 0.00-0.63). CHAQ and HAQ scores combined did not change between the follow-up at 15, 27 months and the long-term evaluation (p=0.686 for comparison with the 27 month measurement). Level of disability was low, 18 patients (42%) had a CHAQ/HAQ score of 0. VAS pain (median 12, IQR: 2-43) and VAS wellbeing (median 16, IQR: 3-41) were significantly higher than the

earlier measurements when entered into a linear mixed model (p=0.003 and p=0.037 for comparison with the 27 months measurement). They were however still significantly lower than those at start of etanercept (median 65 and median 51 respectively, p<0.001 for both).

Quality of life - generic HRQoL

Figure 1A shows the scores of patients at different time points on the identical domains of the CHQ/SF-36; it includes the norm scores for the Dutch population for the age group 16-40 years.[57]

On a utility scale patients maintained the improvement they had shown in the intermediate follow-up at all levels and also at the multi-attribute level, as shown in figure 2A and 2B. Both single and multi-attribute functions did not change between the intermediate and the long-term follow-up measurement in a linear mixed model.

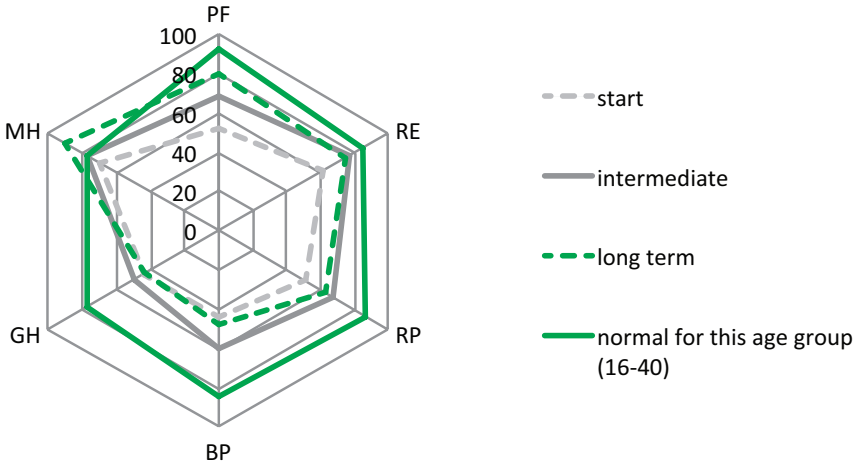


Figure 1A Scores on the six identical domains of CHQ and SF-36 at the different time points
PF=physical functioning, RE=emotional role functioning, RP=physical role functioning, BP=bodily pain, GH=general health perceptions, MH=mental health

The initial improvement in psychological functioning (figure 1B) seemed to continue, although patients did not significantly improve between the intermediate and the long-term evaluation (mean MCS: 57 (±13), p=0.389 for comparison with the 27 month measurement). Physical functioning improved during the first years of follow-up, but remained at a lower level than the general population at the intermediate and long-term evaluation (mean PCS: 33 (±16), p=0.175 for comparison of the long-term follow-up with the 27 month measurement).

No difference was found in the summary scores at long-term follow-up between non-responders and responders to etanercept, nor was there a difference between patients with and without structural damage (data not shown).

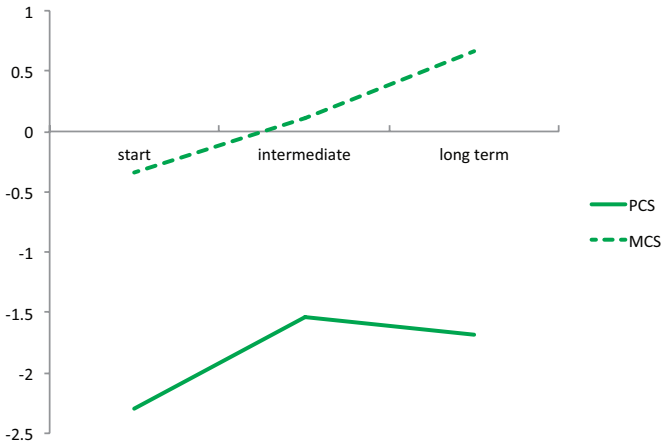


Figure 1B Summary scores of physical (PCS) and psychological (MCS) functioning in standard deviations from normal at the different time points

On a utility scale patients maintained the improvement they had shown in the intermediate follow-up at all levels and also at the multi-attribute level, as shown in figure 2A and 2B. Both single and multi-attribute functions did not change between the intermediate and the long-term follow-up measurement in a linear mixed model.

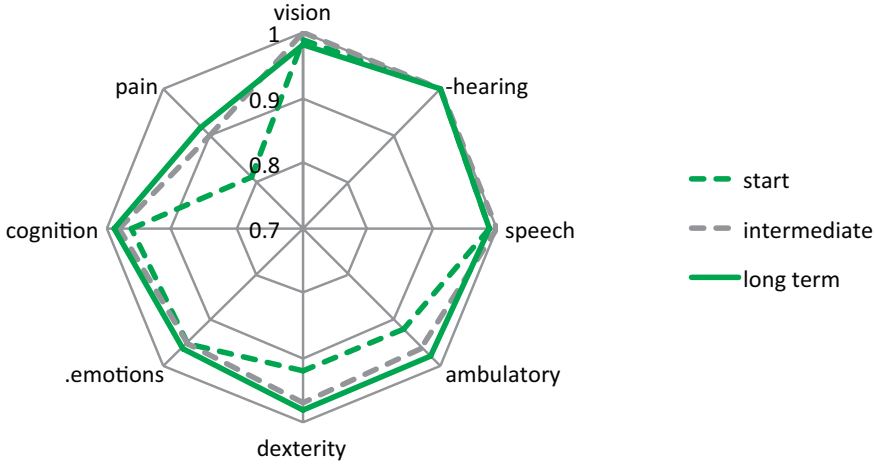


Figure 2A Health Utility Index mark 3 (HUI3) – single attribute function

Changes in the single-attribute functions of the HUI3 at three different time points (range 0 (death) to 1 (perfect health)).

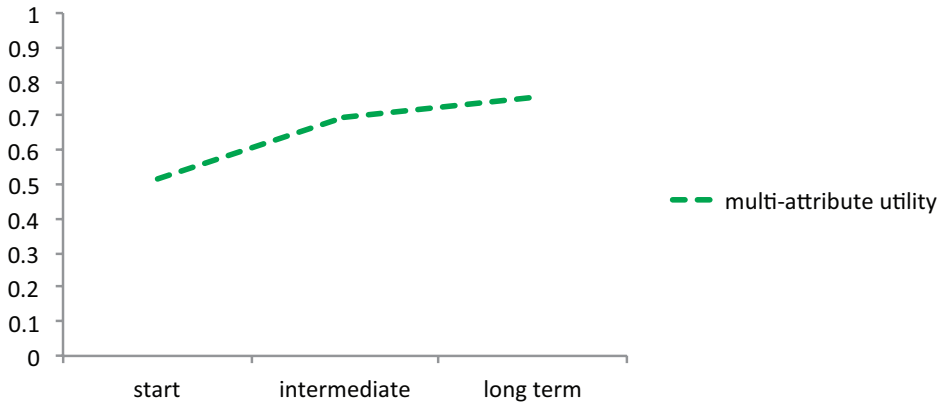


Figure 2B Health Utility Index mark 3 (HUI3) – multi-attribute function
Changes in the multi-attribute function of the HUI3 at three different time points (range 0 (death) to 1 (perfect health)).

DISCUSSION

The objective of this study was to longitudinally investigate the long-term follow-up of biologic-naïve JIA patients treated with etanercept, with a special focus on HRQoL. After a median of 8.5 years, HRQoL on most physical health domains was comparable to the initial response seen after the start of etanercept. Domains related to mental health had improved even further. This suggests that the gain in HRQoL as shown by our research group was maintained.[24] On other aspects of daily life, such as employment and education, patients functioned comparably to or better than their peers. Nevertheless, half of our patients had developed structural damage related to JIA, signs of which were often already present before start of etanercept. Articular damage was reported in part of our patients (mostly with systemic JIA), and some even needed joint surgery despite successful treatment with etanercept or other biologicals.
The majority of patients did not switch to other biologic agents; 40% of patients were still treated with etanercept at the long-term follow-up measurement. At last follow-up, almost 20% of the patients were not using any anti-rheumatic treatment. This is remarkable, considering these patients were all refractory to conventional DMARD treatment.

Comparison to other studies - HRQoL

Two studies investigated long-term HRQoL in JIA patients before biologic agents were available (n=44 and n=82).[52 64] Only one other study investigated long-term disability and HRQoL in the biologic era.[53] This last study had a response of only 56%, and the risk of selection bias towards the severe end of the JIA spectrum is therefore high. The patients studied differed between all publications with regard to age and included JIA categories, due to the setting from which patients were selected. This is especially true for the study by Peterson et al., as it included a large proportion of patients with oligoarticular JIA (73%), who are known to have a better long-term prognosis.[52] These differences should be taken into account, when comparing these cohorts to our patients. The characteristics of the patients included in all four studies (including the present one), HAQ scores and HRQoL scores on the SF-36 are reported in the table in the supplementary files.

The patients included in the study by Peterson et al.[52] seem too different from the other three to really be used as a comparison cohort. The other three studies are quite similar with regard to HRQoL scores. It appears that patients in the current study are functioning better than the patients who did not have access to biologic treatment,[64] but somewhat less than the patients in the more recent study by Minden et al.[53] However, the differences are small. Our patients differ most evidently in the domain for mental health, where they functioned particularly well; and the domain of bodily pain, where our patients scored lowest.

Patients reported as much bodily pain on the SF-36 as they did at start of etanercept, the level was comparable to that reported in the study by Foster at al.[64] We were surprised that patients reported pain despite successful treatment. The other indices for pain in our study only partly showed the same result. The VAS pain also showed an increase between the intermediate and the long-term follow-up, but did not increase to the level at start. The single attribute utility for pain on the HUI3 remained around the same level. This discrepancy may be related to the different ways these questionnaires assess pain. Overall, it seems that pain perception might not be consistent with the presence of active inflammation, as is also suggested by other studies.[6 65-67] Our findings indicate that even when the disease activity is decreased by medication, the pain our patients perceive still affects their HRQoL.

Compared to other studies, outcomes on education and employment of our patients are favourable. Our patients had achieved higher education level compared to their peers from the general population, which is consistent with findings by Packham et al.[68] However, in that study, also a high unemployment level was found in adult JIA patients, which was

confirmed by other studies.[52 53 64 68] In our study, unemployment is in accordance with the employment rate of the general population, although half of our patients did feel limited in their choice of work or education.[63]

Although half of our patients had acquired some form of structural damage, the percentage needing joint surgery was surprisingly low compared to other studies.[53] It has to be taken into account that some of these studies included older patients with a longer disease duration. Most physicians will wait as long as possible to perform a join replacement. Most of the patients with radiological damage already showed signs of this on radiographs taken before the start of etanercept and in the majority this damage remained present or even worsened, despite treatment. It has to be said that radiological damage was not quantified using a standardized scoring method. Therefore we cannot be definite on progression or improvement of radiological damage. The fact that part of patients did need surgery however, does stress the need for early aggressive treatment to achieve and maintain remission as early as possible, preferably before radiological damage is present, to prevent disability due to joint destruction in the long run.

The majority of our patients had inactive disease, which is noteworthy considering these patients were previously refractory to conventional DMARD treatment. Inactive disease was much less common in the study by Minden et al., which is probably caused by a selection bias in that study.[53] Most of our patients were still in rheumatologic care and using anti-rheumatic medication. Remission off medication, the treatment goal, was therefore not yet reached. Nonetheless, this finding shows that even in these patients, remission on medication is an achievable goal.

Strengths and limitations of the study

This is the first study investigating HRQoL and other long-term outcomes of patients starting etanercept in a longitudinal fashion. The response rate was high, which reduces possible selection bias. It may however be that some selection bias was already introduced in the previous study, as the response rate in that study was 75%. This could be reflected for instance in the high educational level of our patients. It is possible that the patients included in the current study are patients who are very willing to take part in research and are therefore different from the patients we already lost in the first stage of this project.

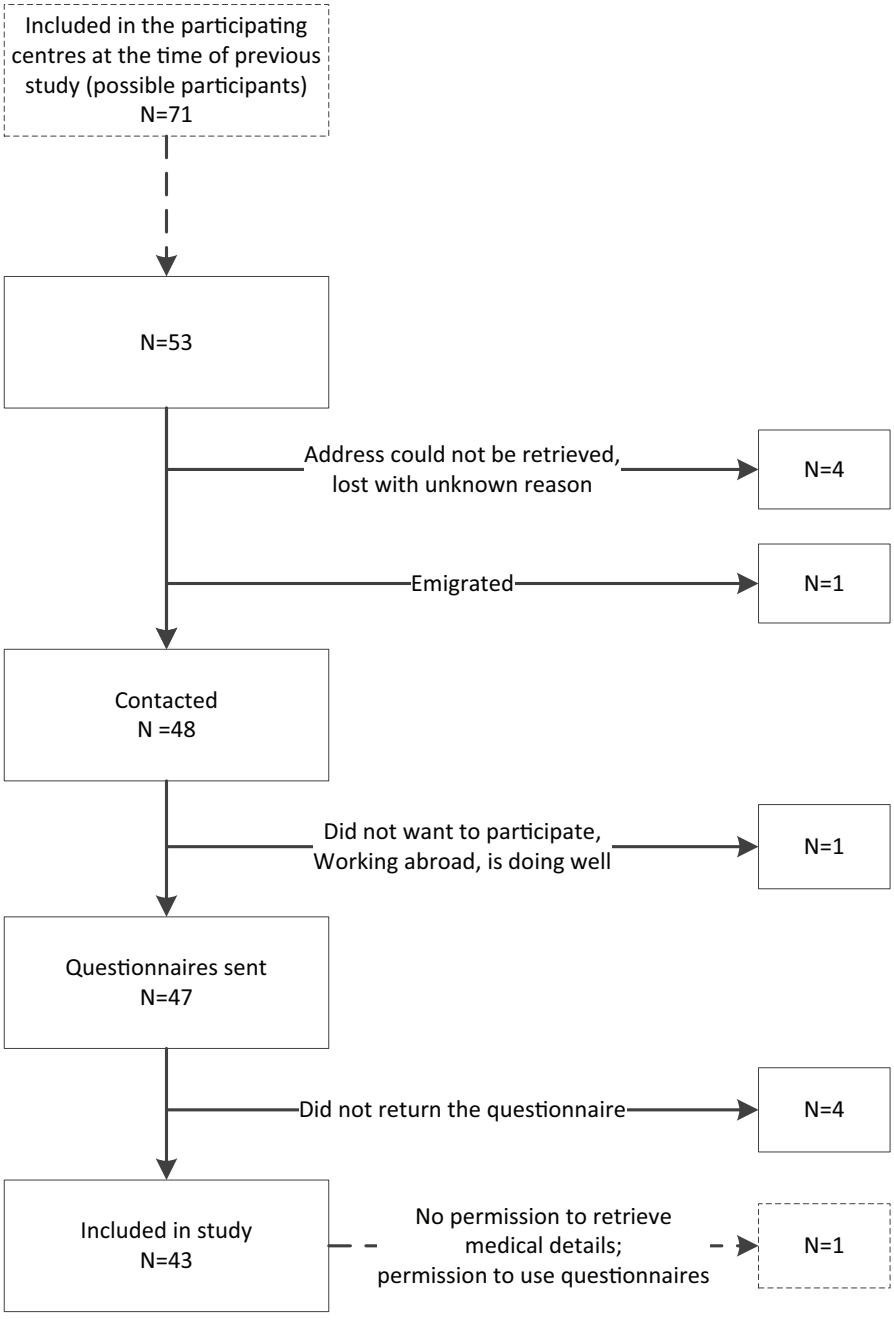
We studied the same patients longitudinally; however there was a large gap between the last intermediate follow-up and the long-term follow-up moment. Some information had to be gathered retrospectively from the rheumatologists, and may therefore be less reliable. An ideal longitudinal study would follow patients through the transition from

paediatric to adult care, recording data also on this important phase. Following patients from childhood into adulthood poses some difficulties regarding outcome measures, as currently few questionnaires are suitable both for paediatric and adult patients. Even when two questionnaires measure the same construct (as is the case with the CHAQ and HAQ questionnaire), this does not mean that the two questionnaires will have perfect agreement.[69]

Conclusions

Concluding, JIA patients treated with etanercept maintain most of the improvement in HRQoL seen after the start of etanercept. Although disability scores are low, chronic pain is an issue that needs to be addressed. Early radiological changes were present at start of etanercept, leading to surgery in 14% of patients in later life, despite effective treatment. This stresses the importance of early treatment of JIA, before radiological damage is present, and the need to treat towards disease remission. Since part of our patients were able to stop all anti-rheumatic medication, clinical remission off medication seems to be an achievable goal, even for this group long thought to be refractory to all medication.

SUPPLEMENTARY TEXT: FLOW CHART



SUPPLEMENTARY TEXT: DESCRIPTION OF HRQOL QUESTIONNAIRES

SF-36 (Medical Outcomes Short Form 36)

The SF-36 is one of the most widely used generic HRQoL measures and has been validated in the general population in the Netherlands.[57] Additionally, several studies validated the use of the SF-36 in rheumatic diseases, and it is used in most studies in RA that reported a HRQOL measure.[70-74] The SF-36 assesses eight aspects of health; physical functioning (PF), role functioning: emotional limitations (RE), role functioning: physical limitations (RP), bodily pain (BP), general health perceptions (GH), mental health (MH), vitality (VT) and social functioning (SF). These health concepts can be summarized in two domains; physical and emotional functioning (PCS and MCS). It is designed for use in adults. Scores on both the SF-36 and the CHQ are scaled from 0 to 100, with 100 indicating perfect health.

CHQ (Child Health Questionnaire)

The CHQ is a generic health measure closely related to the SF-36, but specifically designed for the use in younger patients. We applied the Dutch proxy version (CHQ-PF50).[60] The CHQ assesses 13 health concepts; physical functioning (PF), role functioning: emotional/ behavioral limitations (REB), role functioning: physical limitations (RP), bodily pain/ discomfort (BP), general health perceptions (GH), mental health (MH), general behavior perception (BE), self-esteem (SE), change in health (CH), emotional impact on the parent (PE), impact on the parent's personal time (PT), limitations on family activities (FA) and family cohesion (FC). Also from these concepts two summary scores can be calculated (PCS and MCS).

HUI3 (Health Utility Index Mark 3)

The HUI3 is a preference-based HRQoL measure that classifies level of impairment in eight domains (attributes) based on information retrieved by a 15-item questionnaire. These single attributes are vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, with each five or six levels representing the range of functioning from not impaired (1) to severely impaired (5 or 6). Subsequently, single and multi-attribute utilities can be assigned to the scoring on the HUI3. [62] These utilities are scored on a scale from 0 (dead) to 1 (perfect health).

SUPPLEMENTARY TABLE OVERVIEW STUDIES HRQOL AND DISABILITY

	Study (year, n) Peterson[52] (1997, 44)	Foster[64] (2003, 82)	Minden[53] (2012, 346)	Anink (2014, 43)
Patient selection	Population-based	(Adult) clinic-based	Register-based (etanercept)	Register based (etanercept)
Design	Cross sectional	Cross sectional	Cross sectional	Longitudinal
Response, %	88	82	56	81
Age	34 (mean)	30 (median)	21 (median)	22 (median)
JIA Categories (%)				
Systemic JIA	11	15	7	28
Polyarticular RF negative JIA	16	24	26	28
Polyarticular RF positive JIA		15	16	16
Oligoarticular Extended JIA	73	10	15	19
Oligoarticular persistent JIA		16	3	-
Psoriatic JIA	NA	9	11	7
ERA	NA	12	22	2
Undifferentiated JIA	NA	-	4	-
HAQ score > 0, %	±35	>50	51	58
Domain SF-36, mean*				
PF	86	53	78	79
VT**	56	50	55	70
BP	78	51	65	48
GH	67	50	54	53
RP	87	62	77	66
SF**	91	76	84	80
RE	86	77	86	80
MH	77	71	71	89
Summary score SF-36***				
PCS	NA	40	45	33
MCS	NA	52	56	57

HRQoL=health related quality of life, JIA=juvenile idiopathic arthritis, HAQ=health assessment questionnaire, PF=physical functioning, RE=emotional role functioning, RP=physical role functioning, BP=bodily pain, GH=general health perceptions, MH=mental health, PCS=physical component summary score, MCS=mental component summary score

*Mean scores for the study by Anink et al. are based on combined scores from CHQ for patients < 17 years of age (n=8) and scores from SF-36 for patient >17 years of age (n=35).

**Mean scores for the study by Anink et al. on the domains vitality and social functioning are based only on patients > 17 years old.

***For the study by Foster et al. the summary scores for patients < 30 years of age are reported.

Chapter 3. **Increasing options in biologic treatment: what to do?**

Chapter 3.1 **Trends in prescription of biologic agents**

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ABSTRACT

Background. Treatment of juvenile idiopathic arthritis (JIA) has changed dramatically since the introduction of biological agents in 1999.

Objectives. To evaluate trends in prescription patterns of biological agents and the subsequent outcome of JIA.

Methods. The ABC register (multicentre prospective observational study) aimed to include all consecutive patients with JIA in the Netherlands who had started biological agents since 1999. Patients were divided according to year of introduction of first biological agent. Patient characteristics at introduction of the first biological agent and its effectiveness were analysed over 12 years.

Results. 335 patients with non-systemic JIA and 86 patients with systemic JIA started a biological agent between 1999 and 2010. Etanercept remained the most often prescribed biological for non-systemic JIA; anakinra became first choice for systemic JIA. The use of systemic glucocorticoids and synthetic disease-modifying anti-rheumatic drugs before biological agents decreased. During these 12 years of observation, biological agents were prescribed earlier in the disease course and to patients with lower baseline JADAS (Juvenile Arthritis Disease Activity Score) disease activity. All baseline disease activity parameters were lowered in patients with non-systemic JIA. In systemic JIA, prescription patterns changed towards very early introduction of biological agents (median 0.4 years of disease duration) in patients with less severe active arthritis and high erythrocyte sedimentation rate levels. These changes for both systemic and non-systemic JIA resulted in more patients with inactive disease after 3 and 15 months of treatment.

Conclusions. Biological agents are increasingly prescribed, earlier in the disease, and in patients with JIA with lower disease activity. These changes are accompanied by better short-term disease outcomes.

INTRODUCTION

Treatment of juvenile idiopathic arthritis (JIA) has changed dramatically since the introduction of biological agents in 1999. An increasing number of biological agents targeting different cytokines, such as tumour necrosis factor α, interleukin (IL)-1 and IL-6, have become available during the past decade. Recently, studies have shown that earlier and more aggressive treatment for JIA may result in better outcomes.[29 75-78] The treatment goal has moved to the achievement of inactive disease with prevention of structural joint damage and functional decline. Whether the new insights into the treatment of JIA have led to changes in prescription of biological treatment in daily practice and have affected the outcomes of JIA is still largely unknown.

We evaluated the use of biological agents, the patient characteristics and disease outcomes in the Dutch JIA patient population who started their first biological agent between 1999 and 2010.

METHODS

The Dutch national Arthritis and Biologicals in Children (ABC) register

The ABC register is a multicentre prospective observational study that aimed to include all patients with JIA in the Netherlands who started biological agents. This register was founded in 2003 and contains prospectively collected data since 1999. Between 1999 and 2008 data collection on patients starting biological treatment was required for reimbursement. This resulted in a high awareness of the register even after 2008 to include all consecutive patients. Patients enrolled in clinical trials could not be included in the ABC register because of competing interests. The study protocol was approved by the Medical Ethics Committee at Erasmus MC Rotterdam and by all participating hospitals.

Patient selection and assessments

This analysis was limited to biologically-naïve patients who started their first biological agent between 1999 and 2010. We excluded patients with uveitis as the only indication for starting a biological agent.

Patient and disease characteristics at baseline and after 3 and 15 months of treatment were analysed. Disease characteristics include the JIA core set variables: physician's global assessment of disease activity on a visual analogue scale (VAS) (range 0-100 mm, 0 best score), Childhood Health Assessment Questionnaire (CHAQ) (range 0-3, 0 best

score) by patients/parents, including global assessment of wellbeing and pain by a VAS, number of joints with active arthritis, number of joints with limited motion and erythrocyte sedimentation rate (ESR). The modified definition for inactive disease was specified as no active arthritis, no systemic features, no uveitis, normal ESR (≤ 20 mm/h) and physician's global assessment of disease activity indicating no disease activity (defined as a score ≤ 10 mm).[45] JADAS-10 (Juvenile Arthritis Disease Activity Score) ranges from 0 to 40 and is calculated as the simple linear sum of the scores of the physician and parent/patient global assessment (VAS 0-10), the reduced 10-active joint count and a normalised value of ESR on a 0-10 scale.[23]

Analysis

To investigate time trends, patients were divided in time periods according to the year of introduction of their first biological agent. Results for the years 1999 and 2000 were combined, because the first biological agent became available in 1999 and reimbursement started in 2000. Results for patients with systemic JIA and patients with non-systemic JIA categories (i.e., all JIA categories besides systemic JIA) were presented separately. Descriptive statistics are reported as absolute frequencies, or as median values with an IQR. Treatment effect was evaluated using drug survival and the achievement of inactive disease and the JADAS-10 score. One-year and 2-year drug survival were estimated using Kaplan-Meier analysis. To account for patients who had withdrawn from treatment, the LUNDEX-corrected inactive disease was calculated by multiplying the fraction of patients still receiving the drug with the proportion of patients with inactive disease after 3 and 15 months, respectively.[79]

Analyses of time trends were performed for continuous variables with the Jonckheere-Terpstra test for trend, for categorical variables with the linear-by-linear association test and for data regarding drug survival with a Cox proportional hazards model with the year of start as covariate.

A second analysis was conducted to identify patients in homogeneous clusters for values of the JADAS-10; the JIA core set variables and disease duration at time of introduction of the first biological agent. The two-step auto-cluster procedure developed by SPSS was used to identify the optimal number of clusters based on the Akaike Information Criterion (AIC, a measurement of goodness of fit) together with the log-likelihood criterion as distance measure. Additional baseline characteristics and treatment outcomes were compared among patients within the different clusters.

Missing were 11.7% of variables of the JIA core set (including VAS pain), with a mean of

0.8 variables (SD ±1.6) per core set. If a minimum of three (out of seven) variables per core set was present, the remaining variables were imputed with the aregImpute function of the R statistical package. One of the imputed datasets was used to perform the analysis. All reported p-values were based on two-sided tests for significance, and p-values <0.05 were considered statistically significant. SPSS V.20.0 and R statistical package 2.12.1 were used for the analyses.

RESULTS

A total of 335 patients with non-systemic JIA and 86 patients with systemic JIA started their first biological agent between 1999 and 2010. The number of biologically-naive patients with JIA who started a biological agent increased from 12 in 1999-2000 to 82 in 2010, as shown in figure 1.

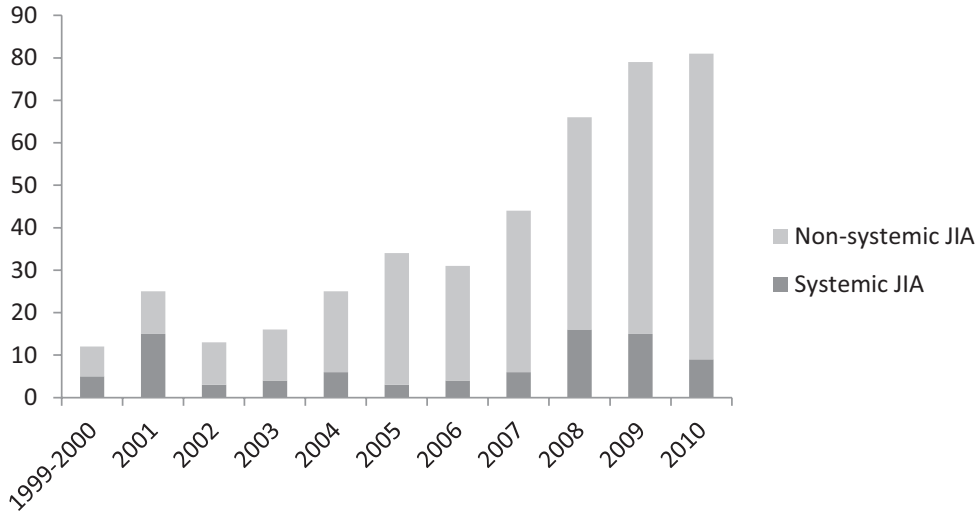

Figure 1 Number of biologically naive patients with non-systemic and systemic juvenile idiopathic arthritis (JIA) who started biological treatment between 1999 and 2010.

Non-systemic JIA categories

For each year, patient characteristics at baseline and outcomes after 3 and 15 months are presented in table 1. During the first years etanercept was prescribed almost exclusively. In 2010, most patients (90%) started etanercept and 9% of patients started adalimumab. Furthermore, the use of systemic corticosteroids before introduction of biological agents

decreased (76% in 1999-2001 to 38% in 2008-2010), as well as the use of other sDMARDs besides methotrexate (76% in 1999-2001 to 33% in 2008-2010). In the first 5 years, it was mainly patients with JIA with a polyarticular course who were treated with biological agents. More recently, patients with other categories of JIA have started biological treatment. Over time, biological treatment has been started earlier in the disease course; disease duration before the start of treatment has changed significantly from a median of 6.9 years (IQR 4.9-11.9) in 1999-2001 to 2.2 (1.2-4.9) in 2008-2010. Lower disease activity was seen in patients who started biological agents in more recent years (Table 1).

Of patients who started treatment between 1999 and 2010, disease outcome improved after 3 and 15 months of treatment; although median JADAS-10 scores decreased non-significantly, an increasing proportion of patients fulfilled the inactive disease criteria according to Wallace (Figure 2). Drug survival after 1 and 2 years of treatment was 87% and 75% overall and did not change (p=0.16 and p=0.20).

Because disease activity and disease duration at baseline differed significantly over time, a cluster analysis was performed to identify more homogeneous groups of patients. The patient and disease characteristics of the three resulting clusters of patients are presented in Table 2. The level of JADAS-10 at baseline was found to be the most important distinguishing factor between the clusters. Cluster 1 represents patients with lower disease activity at baseline (mean JADAS-10: 12 (95% CI 11 to 13)); cluster 2 patients with moderately high disease activity (mean JADAS-10: 18 (95% CI 17 to 19) and cluster 3 represents patients with the highest disease activity (mean JADAS-10: 25 (95% CI 24 to 26)). Disease duration did not differ significantly between clusters and was the least important clustering variable. Outcomes of the three clusters were different. Patients with higher disease activity at baseline less often achieved inactive disease and discontinued the first agent more often because of ineffectiveness or intolerance.

Table 1 Characteristics and outcomes of non-systemic JIA patients considered for biological treatment between 1999 and 2010

Patient characteristics at baseline	1999-2001	2002- 2004	2005-2007	2008-2010	p for trend
	N=17	N=41	N=96	N=181	
Female	15 (88)	30 (73)	73 (76)	120 (66)	0.02
Age onset JIA, median (IQR), years	3.4 (2.0-6.3)	8.0 (3.9-11.0)	8.2 (3.8-11.4)	8.5 (3.0-11.9)	0.64

Disease duration before start, median (IQR), years	6.9 (4.9-11.9)	3.4 (2.0-7.3)	3.0 (1.5-7.0)	2.2 (1.2-4.9)	0.005
JIA category					
Polyarticular RF+	3 (18)	5 (12)	8 (8)	20 (11)	-
Polyarticular RF-	9 (53)	24 (59)	41 (43)	76 (42)	-
Oligoarticular extended	4 (24)	6 (15)	31 (32)	39 (22)	-
Oligoarticular persistent	-	-	1 (1)	18 (10)	-
Psoriatic Arthritis	-	4 (10)	9 (9)	11 (6)	-
ERA	1 (6)	2 (5)	6 (6)	16 (9)	-
Undifferentiated arthritis	-	-	-	1 (1)	-
Medication history before introduction of first biological agent					
Systemic steroid	13 (76)	18 (44)	38 (40)	68 (38)	0.004
Methotrexate	13 (76)	34 (83)	86 (90)	181 (100)	0.46
Other sDMARDs (besides methotrexate)	13 (76)	22 (54)	48 (50)	60 (33)	<0.001
First biological agent started					
Etanercept	17 (100)	40 (98)	93 (97)	166 (92)	-
Adalimumab	-	-	1 (1)	12 (7)	-
Infliximab	-	1 (2)	2 (2)	3 (2)	-
Disease activity at baseline					
Physician's global assessment, median (IQR)	75 (45-83)	70 (56-80)	60 (46-71)	50 (35-65)	<0.001
Number of active joints, median (IQR)	18 (10-23)	12 (8-22)	10 (6-17)	6 (3-10)	<0.001
Number of limited joints, median (IQR)	12 (7-16)	8 (4-15)	7 (4-14)	3 (1-6)	<0.001
CHAQ score, median (IQR)	1.8 (1.2-2.2)	1.8 (1.0-2.4)	1.5 (1.0-2.0)	1.1 (0.5-1.8)	<0.001
VAS pain, median (IQR)	53 (26-75)	52 (20-74)	60 (37-76)	52 (22-72)	0.021
VAS well-being, median (IQR)	60 (27-71)	51 (27-74)	61 (36-75)	50 (21-70)	0.001
ESR, median (IQR), mm/h	22 (9-39)	25 (12-35)	18 (8-31)	11 (6-26)	<0.001
JADAS-10, median (IQR)	22 (19-25)	21 (18-26)	21 (16-24)	16 (12-21)	<0.001

Results are shown as numbers of patient (%) unless stated otherwise.

CHAQ=childhood health questionnaire; ERA=enthesitis related arthritis; ESR=erythrocyte sedimentation rate; JADAS=Juvenile Arthritis Disease Activity Score; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; sDMARD=synthetic disease modifying drugs; VAS=visual analogue scale

Table 2 Cluster analysis of non-systemic JIA patients

	Cluster*			p-value†	Importance of variable in cluster differentiation (1-0)
	1 (N=96)	2 (N=137)	3 (N=95)		
Variables of the JIA core set at baseline					
Physician's global assessment, mean (95% CI), range 0-100	42 (37-47)	51 (48-54)	71 (68-73)	<0.001	0.37
CHAQ score, mean (95% CI), range 0-3	0.71 (0.60 to 0.82)	1.40 (1.29 to 1.51)	1.97 (1.85 to 2.09)	<0.001	0.54
VAS pain, mean (95% CI), range 0-100	19 (16 to 22)	59 (56 to 62)	71 (67 to 76)	<0.001	0.87
VAS wellbeing, mean (95% CI), range 0-100	17 (14 to 19)	60 (57 to 64)	69 (64 to 74)	<0.001	0.90
Number of joints with active arthritis, mean (95% CI)	6 (5 to 7)	7 (6 to 8)	21 (18 to 23)	<0.001	0.67
Number of joints with limited motion, mean (95% CI)	4 (3 to 5)	5 (4 to 6)	15 (13 to 16)	<0.001	0.52
ESR, mean (95% CI), mm/h	17 (15 to 20)	19 (16 to 22)	28 (23 to 33)	<0.001	0.06
JADAS-10, mean (95% CI), range 0-40	12 (11 to 13)	18 (17 to 19)	25 (24 to 26)	<0.001	1.00
Disease duration before start, mean (95% CI), years	4.6 (3.9 to 5.3)	4.2 (3.6 to 4.8)	3.9 (3.2 to 4.7)	0.475	0.01
Additional characteristics and measurements					
Female (n=237)	66 (69)	97 (71)	70 (74)	0.557	
JIA categories					
Polyarticular RF- (n=150)	38 (40)	52 (38)	58 (61)	0.001	
Polyarticular RF+ (n=36)	7 (7)	16 (12)	13 (14)	0.312	
Oligoarticular extended (n=81)	29 (30)	38 (28)	13 (14)	0.016	
Oligoarticular persistent (n=20)	11 (12)	7 (5)	-	0.001	
Psoriatic Arthritis (n=24)	6 (6)	9 (7)	7 (7)	0.902	
ERA (n=23)	5 (5)	14 (10)	4 (4)	0.144	
Undifferentiated arthritis (n=1)	-	1 (1)	-	-	
Year of start biological treatment, median (IQR)	2009 (2006-2010)	2008 (2007-2009)	2006 (2004-2008)	<0.001	

Number of patients with inactive disease after 3 months (n=73 of 305 patients with measurement at 3 months)	28 (32)	28 (20)	17 (19)	0.036	
Number of patients with inactive disease after 15 months (n=100 of 236 patients with measurement at 3 months)	42 (59)	33 (37)	25 (33)	0.002	
% of patients still on drug after 1 year	91	88		84	0.051

On the basis of the JIA core set variables and disease duration before start first biological agent (i.e., at baseline), cases were assigned to cluster groups with the use of the two-step auto-cluster procedure developed by SPSS. This procedure selected three cluster groups on the basis of AIC and the ratio of distance measures

* Seven patients were excluded because of outlying or missing values

† p Values on the basis of analysis of variance(differences of mean values of JIA core set at baseline), Kruskal-Wallis test (non-parametric, continuous variables), Pearson χ^2 test (non-parametric, categorical variables) or Log rank (drug survival analysis)

AIC=Akaike information criterion; CHAQ=childhood health questionnaire; ERA=enthesitis related arthritis; ESR=erythrocyte sedimentation rate; JADAS=Juvenile Arthritis Disease Activity Score; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; sDMARD=synthetic disease modifying drugs; VAS=visual analogue scale.

Systemic JIA

The characteristics and disease outcome of patients with systemic JIA who started a biological agent between 1999 and 2010 are reported in Table 3. Until 2007 etanercept was most frequently prescribed for systemic JIA in the Netherlands. In 2008 anakinra became the preferred choice and biological treatment was started earlier (after median of 0.4 years of disease duration). In half of patients it was started even before the use of corticosteroids and synthetic disease-modifying anti-rheumatic drugs. Over time biological treatment was started in patients with less severe arthritis. Patient-reported indices (VAS pain and VAS well-being) remained similar. The ESR was significantly higher in patients included in later years.
While at baseline JADAS-10 did not differ significantly, after 3 months of treatment JADAS-10 decreased from a median of 15 (IQR 9-26) points in the years 1999-2001 to 1 (IQR 0-5) points in 2008-2010. As in the group with non-systemic JIA, more patients achieved inactive disease after 3 and 15 months of treatment during more recent years (Figure 2). Overall drug survival was 71% after 1 year and 65% after 2 years, and did not change over time (p=0.14 and p=0.19).
For the same reasons as in the non-systemic JIA categories, cluster analysis was performed, identifying three clusters of patients with systemic JIA. The characteristics

of the patients classified in these clusters are presented in Table 4. Most important distinguishing factors were the number of active joints and the JADAS-10 score. Cluster 1 comprises patients with relatively low JADAS-scores (mean JADAS-10: 13 (95% CI 11-15)). Cluster 2 consists of patients with high JADAS-scores (mean JADAS-10: 26 (95%CI: 25 to 28)), mostly resulting from high ESR values (mean ESR: 94 mm/h (95% CI 82 to 106)). Patients in clusters 1 and 2 were usually treated later in the study period (median start year 2008). Patients in the third cluster had relatively high JADAS-10 scores (mean: 25 (95% CI 23 to 27)), with these high scores mostly resulting from a severe polyarthritis (mean: 22 joints with arthritis (95% CI 19 to 26)). These were the patients treated in the earlier years (median start year 2001), when biological treatment had just become available. This last cluster seems to have the worst outcome, with only 5% of patients achieving inactive disease after 3 months.

Table 3 Characteristics and outcomes of patients with systemic JIA starting biological treatment between 1999 and 2010

Patient characteristics at baseline	**1999-2001 N=20**	**2002-2004 N=18**	**2005-2007 N=13**	**2008-2010 N=40***	**p for trend**
Female	10 (50)	8 (62)	10 (77)	17 (43)	0.65
Age onset JIA, median (IQR), years	4.5 (2.8-5.5)	5.2 (2.5-10.6)	4.9 (3.8-11.1)	5.4 (2.4-11.0)	0.31
Disease duration before start, median (IQR), years	3.5 (2.2-5.2)	1.9 (1.0-4.3)	1.5 (0.9-7.5)	0.4 (0.1-1.6)	<0.001
Medication history before introduction of first biological agent					
Systemic steroid	18 (90)	13 (100)	13 (100)	20 (50)	<0.001
Methotrexate	19 (95)	13 (100)	13 (100)	24 (60)	0.001
Other sDMARDs (besides methotrexate)	6 (30)	3 (23)	4 (31)	3 (8)	0.02
First biological agent started					
Etanercept	18 (90)	13 (100)	11 (84)	11 (28)	-
Anakinra	-	-	2 (15)	29 (73)	-
Infliximab	2 (10)	-	-	-	-
Disease activity at baseline					
Physician's global assessment, median (IQR)	72 (52-82)	69 (57-72)	63 (36-84)	40 (29-53)	<0.001
Number of active joints, median (IQR)	18 (9-26)	13 (8-20)	6 (4-10)	3 (2-5)	<0.001
Number of limited joints, median (IQR)	12 (8-17)	9 (6-21)	8 (4-13)	2 (1-4)	<0.001

CHAQ score, median (IQR)	2.2 (1.9-2.6)	2.0 (1.0-2.6)	2.1 (1.1-2.7)	1.8 (0.5-2.4)	0.02
VAS pain, median (IQR)	54 (14-65)	75 (32-88)	70 (39-85)	62 (35-77)	0.44
VAS wellbeing, median (IQR)	41 (9-76)	51 (32-79)	60 (34-88)	60 (27-74)	0.30
ESR, median (IQR), mm/h	45 (24-84)	38 (18-62)	66 (40-91)	101 (28-134)	0.02
JADAS-10, median (IQR)	24 (19-29)	22 (20-26)	25 (15-28)	22 (13-27)	0.06*

One patient was previously diagnosed as systemic JIA in 2006, but diagnosis was changed to poly-articular course JIA in 2008.

CHAQ=childhood health questionnaire; ERA=enthesitis related arthritis; ESR=erythrocyte sedimentation rate; JADAS=Juvenile Arthritis Disease Activity Score; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; sDMARD=synthetic disease modifying drugs; VAS=visual analogue scale.

Table 4 Cluster analysis of systemic JIA patients

	Cluster*			p value†	Importance of variable in cluster differentiation (1-0)
	1 (N=26)	2 (N=37)	3 (N=21)		
Variables of the JIA core set at baseline					
Physician's global assessment, mean (95% CI), range 0-100	34 (27 to 42)	59 (52 to 66)	71 (65 to 78)	<0.001	0.37
CHAQ score, mean (95% CI), range 0-3	0.95 (0.63 to 1.26)	2.09 (1.84 to 2.33)	2.25 (2.01 to 2.48)	<0.001	0.41
VAS pain, mean (95% CI), range 0-100	28 (20 to 37)	76 (71 to 81)	54 (41 to 68)	<0.001	0.53
VAS wellbeing, mean (95% CI), range 0-100	28 (20 to 36)	73 (67 to 79)	44 (28 to 60)	<0.001	0.43
Number of joints with active arthritis, mean (95% CI)	5 (3 to 6)	6 (5 to 7)	22 (19 to 26)	<0.001	1.00
Number of joints with limited motion, mean (95% CI)	4 (2 to 6)	5 (4 to 6)	18 (14 to 22)	<0.001	0.57
ESR, mean (95% CI), mm/h	46 (28 to 63)	94 (82 to 106)	54 (37 to 71)	<0.001	0.24
JADAS-10, mean (95% CI), range 0-40	13 (11 to 15)	26 (25 to 28)	25 (23 to 27)	<0.001	0.72
Disease duration before start, mean (95% CI), years	3.5 (1.8 to 5.2)	1.8 (1.0 to 2.6)	3.7 (2.1 to 5.2)	0.050	0.06

Additional characteristics and measurements				
Female	12 (46)	19 (51)	9 (43)	0.811
% of patients on anakinra	39	51	10	0.005
Year of start biological treatment, median (IQR)	2008 (2003-2009)	2008 (2006-2009)	2001 (2001-2004)	<0.001
Number of patients with inactive disease after 3 months (n=79 patients with measurement at 3 months)	11 (46)	16 (46)	1 (5)	0.006
Number of patients with inactive disease after 15 months (n=69 patients with measurement at 15 months)	12 (55)	14 (44)	6 (29)	0.630
% of patients still on drug after 1 year	81	66	67	0.075

On the basis of the JIA core set variables and disease duration before start first biological agent (i.e., at baseline), cases were assigned to cluster groups with the use of the two-step auto-cluster procedure developed by SPSS. This procedure selected three cluster groups on the basis of AIC and the ratio of distance measures

* Two patients were excluded because of outlying or missing values

† p-values on the basis of analysis of variance (differences of mean values of JIA core set at baseline), Kruskal-Wallis test (non-parametric, continuous variables), Pearson χ^2 test (non-parametric, categorical variables) or Log rank (drug survival analysis)
AIC=Akaike information criterion; CHAQ=childhood health questionnaire; ERA=enthesitis related arthritis; ESR=erythrocyte sedimentation rate; JADAS=Juvenile Arthritis Disease Activity Score; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; sDMARD=synthetic disease modifying drugs; VAS=visual analogue scale.

DISCUSSION

This overview of 12 years' observation of biological treatment in the Netherlands allows us to conclude that biological agents are prescribed more often, earlier and at lower disease activity in patients with JIA. These changes in prescription behaviour of doctors are accompanied by a better short-term disease outcome. Better treatment outcome is mainly seen in patients who have lower disease activity at the start of biological treatment. The group with systemic JIA that starts biological treatment has changed most significantly. Prescription of biological agents for JIA increased over time. This trend is not likely to be influenced by an overall increase in the incidence of JIA; a recent study in a North American population (1996-2009) does not suggest a change in incidence over the years.[79-82] It

is more likely that this trend is the result of the observed effectiveness of the biological treatment, the growing reliance of the doctors on biological agents and the increasing availability of the drugs. Over time, additional biological agents with different mechanisms of action have become available for JIA. During the past 12 years, etanercept remained the preferred choice for patients with non-systemic JIA and adalimumab was mainly prescribed for a subset of patients. Most patients with JIA treated with adalimumab had (a history of) uveitis.[83] Patients with systemic JIA are nowadays more often treated with IL-1 antagonists than tumour necrosis factor α inhibitors. This change in prescribed biological agents for systemic JIA is expected, because increasing knowledge about the immunological pathways involved in the development of arthritis and associated systemic features has resulted in IL-1 antagonists becoming more favoured.[84 85]

Strategies for treatment of JIA are constantly developing. The goal of treatment has moved towards disease remission in all patients. To achieve this, some doctors promote a treat-to-target strategy using an aggressive step-up regimen.[86] The time-trends of prescription earlier in the disease course and at lower levels of disease activity, show us that a more aggressive treatment strategy has been adopted in the Netherlands. That these trends towards a more aggressive treatment are accompanied by better outcomes might support the effectiveness of this approach. We have to keep in mind, however, that this is an observational study and no control group was included. Therefore a causal relation between changing treatment strategies and outcome cannot be assessed. Our results reflect clinical practice and do not investigate very early introduction of biological agents, as researched in the TREAT and ACUTE-JIA studies.[77 78]

This is, to the best of our knowledge, the first study that describes trends in prescription patterns of biological agents and outcomes of JIA. Similar patterns in prescription of biological agents have been described in rheumatoid arthritis (RA). Studies in RA all demonstrated decreasing baseline disease activity and subsequently better clinical outcomes during the observed treatment years.[87-91] Two of these studies in RA found, also, as we did in our study in JIA, a decrease in disease duration before starting biological treatment.[88 92]

The treatment goal of inactive disease has been increasingly achieved during the past 12 years for all JIA categories. This observed trend is likely to be influenced by a changing JIA population for whom biological treatment is prescribed as is also indicated by changing baseline characteristics. Numerous baseline and disease activity variables were tested for trends. Even though 5% of these test results might be spurious, over time a clear tendency towards lower disease activity at baseline and better disease outcomes was seen. Patients

with non-systemic JIA who were included more recently had better outcome, but they might also reflect a patient group who had a better intrinsic prognosis too. For instance, the distribution of JIA categories for which biological agents are prescribed changed, now including more patients with the oligoarticular persistent subtype. The American College of Rheumatology treatment recommendations for JIA focus more on treating according to the level of disease activity rather than treating patients according to JIA category; this trend is also seen in Europe.[17] In this study, we performed a cluster analysis, which identified patients with similar patterns of disease activity and disease duration, which allowed us to compare outcomes in more homogeneous patient groups.

Patients with non-systemic JIA with lower baseline disease activity achieved inactive disease more often. This relationship seemed unaffected by disease duration, which appeared to be the least important factor in cluster formation.

The changes in prescription patterns for patients with systemic JIA are more striking than those for patients with non-systemic JIA and have become most evident since 2008. In the early years biological treatment was reserved for patients with polyarticular course JIA, while now these agents are also prescribed for patients with more prominently present systemic features and less severe arthritis. Over time, in the group with systemic JIA, inactive disease was achieved by an increasing number of patients. The cluster analysis identified one cluster of patients with systemic JIA treated during the earlier years, with mainly polyarthritis, in whom outcomes were worst. Patients in the remaining two clusters were treated more recently and achieved better disease outcomes. These two clusters represent patients with either low disease activity or patients with high JADAS-scores, mainly based on high ESR levels and fewer joints with arthritis. Patients in this last cluster were treated in a more acute phase of the disease and earlier during the disease course. The favourable outcomes in these patients might also in part be related to the natural course of the disease, because it is known that around one-third of patients with systemic JIA have a mono-phasic disease course.[93-95] Detailed evaluation of this group is needed to investigate which factors are contributing to the differences in treatment response.

A strong feature of this observational study is the inclusion of almost all patients with JIA who started biological treatment in the Netherlands, making the role of selection bias negligible. Selection bias may have been introduced by excluding patients participating in clinical trials, although the number of patients included in trials was small, and those patients were from one centre only. The lack of a control group and the observational nature of the study make it difficult to identify a causal relationship between trends in baseline characteristics and a trend in outcome. Besides the trend analysis, we attempted

to shed light on the different profiles of patients included in the study by balancing out two important changing baseline factors: disease activity and disease duration. In this way, treating doctors are provided with profiles they might recognise from their clinical practice. In these clusters, patients from different time periods could be identified, which shows us by an alternative route that the patient population treated with biological agents definitely changed over time. This is an extra indication that any statements of the effect of changing treatment strategies on the outcomes of patients should be made with caution.

In conclusion, since their introduction, biological agents are being prescribed increasingly often and the threshold for prescribing biological treatment has decreased. The patients with JIA who start biological treatment have changed towards a group with lower disease activity and these changes are accompanied by better short-term disease outcomes.

Chapter 3.2 **Treatment choices of paediatric rheumatologists for JIA: etanercept or adalimumab?**

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ABSTRACT

Objectives. To evaluate differences in baseline characteristics between etanercept- and adalimumab-treated JIA patients and to reveal factors that influence the choice between these TNF inhibitors, which are considered equally effective in the recent ACR recommendations for JIA treatment.

Methods. Biologic-naïve JIA patients with active arthritis who started treatment with adalimumab or etanercept between March 2008 and December 2011 were selected from the Dutch Arthritis and Biologicals in Children register. Baseline characteristics were compared. Focus group interviews with paediatric rheumatologists were performed to evaluate factors determining treatment choices.

Results. A total of 193 patients started treatment with etanercept and 21 with adalimumab. Adalimumab-treated patients had longer disease duration prior to the start of biologics (median 5.7 *vs* 2.0 years) and more often a history of uveitis (71% *vs* 4%). Etanercept-treated patients had more disability at baseline (median Childhood Health Assessment Questionnaire score 1.1 *vs* 0.4) and more active arthritis (median number of active joints 6 *vs* 4). The presence of uveitis was the most important factor directing the choice towards adalimumab. Factors specific for the paediatric population—such as painful adalimumab injections—as well as the physician's familiarity with the drug accounted for the preference for etanercept.

Conclusion. Although the two TNF inhibitors are considered equally effective, in daily practice etanercept is most often prescribed; adalimumab is mainly preferred when uveitis is present. In choosing the most suitable biologic treatment, paediatric rheumatologists take into account drug and patient factors, considering newly published data and cautiously implementing this into daily care.

INTRODUCTION

JIA patients refractory to MTX treatment (dosed ≥15 mg/m^2/wk) are eligible for treatment with biologics. In 1999, etanercept, an anti-TNF-α receptor fusion protein, was the first biologic to be approved by the U.S. Food and Drug Administration for the treatment of JIA (in 2000 the European Medicines Evaluating Agency followed). Its efficacy and safety have been demonstrated in a randomized controlled withdrawal trial and several long-term observational studies, including the Dutch Arthritis and Biologicals in Children (ABC) register.[19 40 96] In 2008, a second biologic agent, adalimumab, a monoclonal anti-TNF antibody, was approved for polyarticular JIA after its efficacy was established in a placebo-controlled withdrawal trial.[41] Adalimumab is considered to be the preferred biologic in treating uveitis, a condition strongly associated with JIA.[42 97-100] Observational data on the use of adalimumab for JIA are limited.[101 102]

The ACR recommendations for JIA consider these anti-TNF agents equally.[17] In RA, adalimumab is considered as effective as etanercept.[103] Neither JIA nor adult RA head-to-head trials exist that compare etanercept and adalimumab. When deciding between these biologics, physicians can only rely on limited evidence and have to consider other factors. Qualitative research can provide insight into how and why physicians make decisions when prescribing medication, which cannot be deduced from quantitative studies.[104]

We compared baseline characteristics of biologic-naïve patients initiating adalimumab or etanercept included in the Dutch ABC register to observe the real-life prescription patterns. Additionally we performed focus group interviews with paediatric rheumatologists and rheumatologists to evaluate the factors that determined their treatment choice.

PATIENTS AND METHODS

Patient population and baseline data

This study is part of the ABC register—a national ongoing multicentre study that aims to include all Dutch patients with JIA treated with biologics. The ABC register contains prospectively obtained data since the introduction of etanercept for JIA in 1999. The register was approved by the Medical Ethics Committee at Erasmus Medical Centre and all participating hospitals. Subjects' written consent was obtained according to the Declaration of Helsinki. At baseline, data on demographics and disease characteristics were collected as well as variables of the JIA disease activity core set.[22] At baseline, 9.9% of the variables were missing, with a median of zero missing variables per patient [interquartile range (IQR) 0–1].

For this analysis, we included biologic-naïve patients who initiated etanercept or adalimumab between March 2008 (when adalimumab became available) and December 2011. JIA patients without active arthritis initiating biologics to treat uveitis only were not included in the analyses (as this would have biased the results), nor were patients participating in treatment strategy trials.

Focus-group methods

The qualitative part consisted of two focus group interviews, carried out in autumn 2011. Twenty paediatric rheumatologists and rheumatologists involved in the care of paediatric patients, all members of the Dutch Society for Paediatric Rheumatology prescribing biologic treatment, were recruited by e-mail. Forty percent participated. The first focus group comprised two rheumatologists and three paediatric rheumatologists, and the second comprised three paediatric rheumatologists. The participants worked in six different areas in seven different hospitals.

The first interview lasted 1 h and the second 37 min. Two researchers were present, the moderator (S.G.) and a research physician (J.A.). The interview guide comprised questions on perceived effectiveness, motivation for initiation, experience with the different therapies and possible contraindications. In addition, participants were confronted with data retrieved from the ABC register comparing baseline characteristics of the two patient groups and asked for their interpretation.

J.A. audio-recorded and transcribed the focus group interviews verbatim. Transcripts were checked for accuracy and sent to participants for checking.

Data analysis

Descriptive statistics were presented as absolute frequencies or median values with IQR. Differences in patient and disease characteristics at baseline were compared using Fisher's exact test or Mann–Whitney *U* test whenever applicable. Differences were considered significant at a two-sided *P*-value <0.05. Data were analysed using the SPSS for Windows package, version 17.0.2 (SPSS Inc., Chicago, IL, USA).

For transcript analysis, a phenomenological approach was used.[105] Transcripts were read and reread to get a global impression and subsequently coded following an open coding strategy by J.A. S.G. checked the coding; J.A. and S.G. discussed coding until consensus was reached. Subsequently key units were identified from the codes and summarized in broader themes. A theme was considered more important according to the frequency of occurrence during the interviews. MAXQDA 10 software was used for analysis of qualitative data.

RESULTS

Data from the ABC-register

Patient and disease characteristics are presented in Table 1. A total of 193 previously biologic-naïve JIA patients initiated etanercept and 21 initiated adalimumab. Patients treated with adalimumab had longer disease duration and were more often diagnosed with persistent oligoarticular JIA. Most adalimumab-treated patients (71%) had a history of uveitis. Six patients did not have a history of uveitis and presented with extended oligoarticular (one), PsA (one) and enthesitis-related arthritis (ERA) (four) JIA categories. Etanercept-treated patients had higher disease activity indicated by higher Childhood Health Assessment Questionnaire (CHAQ) scores and more joints with active arthritis.

Table 1 Patient and disease characteristics

Characteristics	ETN (193)	ADA (21)
Median age at onset JIA, years (IQR)	8.3 (2.8–11.6)	7.2 (2.8–11.6)
Median age at start first biologic, years (IQR)	11.9 (7.5–15.0)	12.7 (10.1–15.8)
Female, n (%)	127 (66)	14 (67)
Onset JIA category, n (%)		
Systemic JIA	16 (8)	0 (0)
Polyarticular RF negative	75 (39)	5 (24)
Polyarticular RF positive	23 (12)	0 (0)
Oligoarticular extended	41 (21)	5 (24)
Oligoarticular persistent*	14 (7)	5 (24)
Juvenile arthritis psoriatica	10 (5)	2 (10)
ERA	14 (7)	4 (19)
Median JIA disease duration before start biologic in years (IQR)*	2.0 (1.2–4.7)	5.7 (1.8–8.1)
History of uveitis, n (%)*	7 (4)	15 (71)
ANA positive, n (%)	81/191 (42)	13/20 (65)
HLA B27 positive, n (%)	17/66 (26)	2/10 (20)
RF positive, n (%)	23/181 (13)	0 (0)
Previously used medications, n (%)		
Systemic prednisone	75 (39)	8 (38)
IA prednisone	66 (34)	10 (48)
MTX	193 (100)	21 (100)

Other synthetic DMARDs (besides MTX)	63 (33)	9 (43)
Concomitant co-medication at baseline, n (%)		
Systemic prednisone	41 (21)	1 (5)
IA prednisone	17 (9)	3 (14)
MTX	158 (82)	15 (71)
Other synthetic DMARDs (besides MTX)	10 (5)	2 (10)
Frequency of prescription per year		
March 2008–December 2008	46	1
January 2009–December 2009	60	6
January 2010–December 2010	58	6
January 2011–December 2011	29	8
Median disease activity scores at baseline		
VAS physician (IQR)	50 (36–65)	40 (30–70)
CHAQ total (IQR)*	1.13 (0.50–1.80)	0.40 (0.07–0.94)
VAS pain (IQR)	55 (25–75)	46 (6–65)
VAS well-being (IQR)	50 (24–73)	32 (6–57)
Active joints (IQR)*	6 (4–10)	4 (2–5)
Limited joints (IQR)	3 (1–6)	2 (2–4)
ESR (IQR), mm/h	12 (6–29)	7 (3–21)

* significance level $p<0.05$

ETN=etanercept; ADA=adalimumab; JIA=juvenile idiopathic arthritis; IQR=interquartile range; RF=rheumatoid factor; ERA=enthesitis related arthritis; ANA=anti-nuclear antibodies; DMARD=disease modifying anti-rheumatic drug; VAS=visual analogue scale; ESR=erythrocyte sedimentation rate

Focus-group results

The main factors influencing decision making are presented in Table 2. These factors can be summarized in three broad categories: internal factors (related to the drug, the patient's characteristics or the doctor), external factors (related to brand awareness, governmental regulations and drug availability) and costs.

Table 2 Factors that influence the choice between etanercept and adalimumab mentioned by focus-group participants

Theme
Internal factors
Drug related
Side effects/safety
Short term
Pain/fear
Infection risk equal
Long term
Immunogenicity: more with adalimumab
Growth: unknown influence of adalimumab
Dosage and administration of the drug
Different mechanisms of action
Patient related
Disease characteristics
Uveitis
ERA/ PsJIA/ IBD symptoms
Other categories of JIA
Patient/parents' choice
Low age: etanercept preferred
Wrist involved: etanercept preferred
Doctor related
Personal familiarity, clear preference for etanercept
Amount of published data on the drug
Gaining experience with a new drug
Feeling/morality
External factors
Brand awareness
Governmental regulations
Drug availability
Costs (when other than standard dosing)

ERA=enthesitis related arthritis; PsJIA=juvenile psoriatic arthritis; IBD=inflammatory bowel disease; JIA=juvenile idiopathic arthritis

Pain on injection was the most important drug-related factor mentioned. All physicians agreed that paediatric patients experience the injections of adalimumab as painful. The prefilled formulation of etanercept is also perceived to be irritating; its self-dissoluble formula was therefore preferred by most. The availability of a formulation specifically adapted for paediatric use was seen as an advantage of etanercept. Although adalimumab has recently improved its paediatric formulation, it was thought to be less practical, as it

still contains the adult dose.

The subject of costs featured less prominently in the discussion than other factors. Costs were considered especially important when dosages other than the adult dosage were prescribed. In adult dosage, etanercept and adalimumab are equally expensive.[39] Government regulations with regard to reimbursement were mentioned in relation to costs; if these change, costs could become more important.

Adalimumab was preferred by all physicians when a history of uveitis or active uveitis was present: *'In recent years it has been shown that etanercept might be less effective for uveitis … resulting in the fact that when I am considering prescribing anti-TNF to a child who has or has had uveitis I would choose adalimumab in the first place*'. Two physicians considered it for all patients with a higher risk of developing uveitis.

Treatment with adalimumab was considered in patients with complaints suggestive of IBD, but in whom IBD could not be confirmed. '*We also have—I know, this is absolutely not evidence based—children with nonspecific intestinal complaints. They have been seen by gastro-enterologists, they have had endoscopies, everything, and then, suddenly out of the blue, they are diagnosed with JIA. In that group I am sometimes a little more inclined to prescribe adalimumab*'. Other indications mentioned for prescribing adalimumab rather than etanercept were ERA and PsJIA.

A doctor-related factor that received a lot of attention was experience. For three physicians, gaining experience with a new treatment was a reason to prescribe adalimumab. However, most physicians strongly indicated etanercept to be their first choice, relying heavily on available efficacy data, their personal familiarity with the drug and the favourable safety profile without immunogenicity. The rheumatologists also treating adult RA patients had more extensive experience with adalimumab and were therefore less reluctant to prescribe it to children, as illustrated by this quote: '*we obviously have this long-lasting experience with adalimumab, for me at least [lack of experience] is not a reason not to start treatment with adalimumab in a child*'.

Finally, practising evidence-based medicine featured prominently in the discussions. During the interviews physicians were constantly referring to literature and evidently trying to base their decisions on the latest available data.

No pressure from the industry was noted, apart from a few comments on advertisements received from and questions asked by visiting representatives of pharmaceutical companies. However, three physicians did suggest that marketing and brand awareness played a role: *'to be honest, you do hear the name adalimumab more and more, as a result of which I think: this might be a suitable treatment for this specific patient*'.

DISCUSSION

This study shows that for JIA both etanercept and adalimumab are being prescribed. Focus group interviews identified a preference for etanercept. This was reflected in the absolute numbers, as 90% of the biologic-naïve patients were started on etanercept. Adalimumab-treated patients were characterized by a history of uveitis, longer disease duration and lower disease activity. The presence of uveitis was acknowledged by interviewees to be one of the most important factors that directed their choice towards adalimumab. Painful adalimumab injections and more extensive personal and scientific experience with etanercept were the most important reasons to be reticent with prescription of adalimumab. The observation that JIA-associated uveitis is a reason to consider treatment with biologics is consistent with the literature. In contrast to its proven efficacy in JIA, results for etanercept in the treatment of refractory uveitis are less satisfactory and adalimumab is now preferred for uveitis.[42 97 98 100 106 107] Uveitis develops most often in the oligoarticular categories, which formed the largest part of the adalimumab-treated group. These categories are generally controlled for longer by treatment modalities other than TNF blockers, which may account for the longer disease duration in the adalimumab-treated group. The presence of uveitis may also explain why disease activity scores (related to arthritis) were lower in patients treated with adalimumab.

ERA and PsJIA were overrepresented in the adalimumab-treated group. This is in line with indications to consider adalimumab mentioned during the focus group interviews. Spondylarthritides are associated with psoriasis and IBD, and TNF-α also plays a role in the pathogenesis of psoriasis and IBD. TNF inhibitors seem equally effective for joint symptoms and skin symptoms, but on gut manifestations monoclonal antibodies against TNF-α seem to be more effective.[108 109]

The present study indicates that the process of prescribing new drugs and implementing them in daily care is complex and takes time, a finding also recognized in other qualitative studies investigating prescription patterns.[110-114] Although the ACR recommendations do not differentiate between the two TNF inhibitors, the adaptation of the prescription pattern apparently involves many factors in addition to the effectiveness of the drug for JIA. These factors were put together in three categories: internal factors, external factors and costs.[111] Experience with the drug was considered a major factor. Etanercept has had a head start concerning safety, with over 10 years of safety data compared with only 4 years for adalimumab.

Costs of TNF inhibitors are approximately the same when prescribed in adult dosages and

might therefore play a less important role, especially in older children. Cost is apparently a secondary factor that comes into play when more experience is acquired with the new drug, and this could change when reimbursement regulations change. It could also be that moral resistance is felt against cost-conscious statements, and therefore they are less often mentioned in focus group interviews. Although a notion of cost-effectiveness has to be present, often doctors feel the emphasis should be on patient-centred factors. The fact that brand awareness and pressure from pharmaceutical companies were mentioned infrequently may be related to this same idea, and their influence might therefore be underestimated.

This study is limited in its size. Because only a few patients received adalimumab, these data should be interpreted with caution.

Not all rheumatologists and paediatric rheumatologists invited for focus group interviews were able to participate. Therefore the influential factors identified might not be representative for all Dutch physicians treating JIA patients with biologics. Nevertheless, physicians originated from different regions, covering the whole of the Netherlands. In both interviews, the same considerations were mentioned and we feel no topics were left out.

The researcher who moderated the interview was experienced in qualitative research. She was a rheumatologist herself, which brings a risk of peer review. However, this possible problem was recognized beforehand and she focused on her role as moderator.

In conclusion, both etanercept and adalimumab are prescribed for JIA. Even though both TNF inhibitors are considered equally effective, paediatric rheumatologists still prefer etanercept. Patient characteristics differed between the two treatment groups, the most important being the presence or risk of uveitis in the adalimumab-treated group. In deciding which biologic to prescribe to the biologic-naïve patient, paediatric rheumatologists take into account drug and patient factors to tailor prescriptions. They consider newly published data and cautiously implement this into daily care. Existing experience with an already established drug, in this case etanercept, makes it more difficult to shift preferences. Drug marketing and costs seem to play a minimal role in this process.

Chapter 3.3 **Indirect comparison of the efficacy of biologic agents for JIA**

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ABSTRACT

Objective. Over the past decade, the availability of biological agents for the treatment of juvenile idiopathic arthritis (JIA) has increased substantially. Because direct head-to-head trials comparing these agents are lacking, we indirectly compared their efficacy.

Methods. In a systematic review, all available efficacy data from randomised controlled trials performed in JIA with inclusion of biological agents were retrieved. Indirect between-drug comparisons (based on Bucher's method) were conducted only if trials were comparable with regard to design and patients' characteristics related to treatment outcome.

Results. We identified 11 randomised controlled trials. On the basis of the equality of the trials, six trials were grouped into two networks of evidence. Network 1 included withdrawal trials which evaluated etanercept, adalimumab and abatacept in polyarticular course JIA. Indirect comparisons identified no significant differences in short-term efficacy. Network 2 indirectly compared trials with a parallel study design investigating anakinra, tocilizumab and canakinumab in systemic JIA; no differences in comparative efficacy were identified. Although the two networks were constructed on the basis of comparability, small differences in trial design and case mix still existed.

Conclusions. Because of the small number of trials and the observed differences between trials, no definite conclusions could be drawn about the comparative effectiveness of the indirectly compared biological agents. Therefore, for now, the paediatric rheumatologist has to rely on observational data and safety, practical and financial arguments. Comparability of future trials needs to be improved, and head-to-head trials are required to decide on the best biological treatment for JIA.

INTRODUCTION

Since 1999, the treatment of juvenile idiopathic arthritis (JIA) has been extended with a new category of drugs: biological agents that target different cytokines and different steps in the immune response. Etanercept, a tumour necrosis factor (TNF)-α receptor antagonist, was the first biological agent approved for the treatment of polyarticular JIA. At present, infliximab (TNF-α antibody), adalimumab (TNF-α antibody), anakinra (interleukin (IL)-1 receptor antagonist), canakinumab (IL-1 antibody), rilonacept (IL-1 receptor antagonist), tocilizumab (IL-6 receptor antibody) and abatacept (selective T-cell co-stimulation modulator) are also available options or under investigation for the treatment of JIA. Physicians involved in the treatment of JIA have an increasing number of biological treatment options and choosing between them is often difficult.

The efficacy of each agent has been described in one or more randomised controlled trials (RCTs), but head-to-head trials comparing agents directly are still lacking. A few studies have compared the short-term efficacy of biological agents in patients with rheumatoid arthritis (RA) using indirect comparison methods.[115-120] This technique allows comparison of two biological agents indirectly (i.e., a trial comparing treatment A vs comparator C and treatment B vs comparator C results in a comparison of A vs B), while preserving the randomisation of the originally assigned patient groups.[116 121] Efforts to indirectly compare these agents in JIA are to our knowledge still lacking. We therefore conducted a systematic review and described the RCTs with regard to their design and patient characteristics and, where possible, compared the efficacy of different biological agents indirectly. We hope that these results will eventually guide physicians in their biological treatment choices for JIA.

PATIENTS AND METHODS

Search strategy and selection criteria

A systematic search on PubMed, Embase and Cochrane clinical trials was performed using the terms: ('JIA' OR 'juvenile RA (JRA)') AND 'randomised controlled trial' AND ('tumour necrosis factor' OR 'interleukin-1' OR 'interleukin-6' OR 'etanercept' OR 'adalimumab' OR 'infliximab' OR 'abatacept' OR 'anakinra' OR 'tocilizumab' OR 'canakinumab' OR 'certolizumab' OR 'golimumab' OR 'rituximab' OR 'rilonacept'). See online supplementary text for the detailed search strategy. The search included studies up to and including January 2012. To identify unpublished trials, the trial register clinicaltrials.gov, and abstracts from international rheumatology congresses were searched. We aimed to include the following studies: RCTs

with data on efficacy, comparing a biological agent with control treatment (placebo, synthetic disease-modifying anti-rheumatic drugs (sDMARDs), or a second biological agent), and including patients with JIA (or the previously used criteria for JRA; any onset category).

Data extraction

Two authors (MHO and JA) independently selected the studies from the search and extracted information from published articles and congress abstracts on design, inclusion and exclusion criteria, medication regimens, baseline characteristics and efficacy results during the double-blind phase. Corresponding authors and involved pharmaceutical industries were contacted for any missing data in the publications. Slides of an oral presentation given at an international meeting provided additional information on a selected publication. The trial quality was assessed independently using the Jadad criteria, a widely used five-point score that appraises the quality of trial reporting. The score assesses trial quality on three aspects: randomisation, blinding and handling of withdrawals and drop-outs.[122] If scoring was not unanimous, scoring was discussed with a third person (LWAvS-S). Figure 1 shows the flow of the 685 retrieved citations.

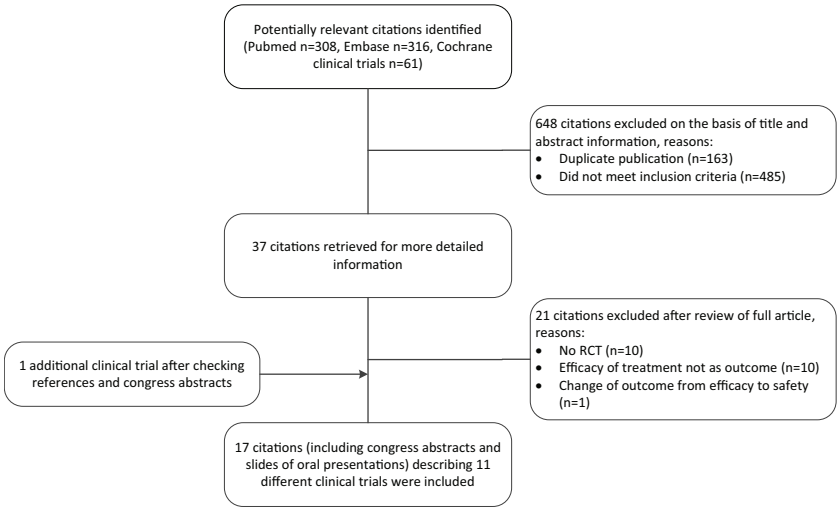

Figure 1 Flow of included studies. RCT=randomised controlled trial.

Trial design

For this systematic review with indirect comparisons, all RCTs conducted with biological agents were included, irrespective of trial design. In the field of paediatric rheumatology,

in general, two different types of clinical trial are conducted. The randomised placebo-controlled withdrawal trial design (called 'withdrawal trial') consists of an open-label lead-in phase where all patients receive the drug. After this lead-in period, only those patients who respond to treatment enter the double-blind phase and are randomised to remain on the drug or receive placebo. For this withdrawal design, the primary outcome chosen is disease flare. The other type of trial used is a 'classic' randomised controlled parallel design. These trials often include concomitant treatment with sDMARDs (e.g., biological agent plus methotrexate vs methotrexate only), short duration of double-blind phase, or a rescue regimen to limit the time without treatment.

Outcome

We identified three major outcomes beforehand: percentage of patients with disease flare and percentage of patients achieving an American College of Rheumatology paediatric (ACRpedi) 30 response or inactive disease. These outcomes are based on changes in the following six variables: physician's global assessment of disease activity on a visual analogue scale (VAS; range 0–100 mm, 0 best score), Childhood Health Assessment Questionnaire (CHAQ; range 0–3, 0 best score) by patients/parents, global assessment of well-being by patients/parents (VAS, range 0–100 mm, 0 best score), number of active joints with arthritis, number of joints with limited motion, and a marker of inflammation (erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)). A disease flare is defined as worsening of 30% or more in at least three of these six variables with an improvement of 30% or more in no more than one variable. An ACRpedi30 response is achieved if three or more of these variables improve by at least 30% from baseline, with no more than one variable worsening by more than 30%.[44] For the systemic JIA category, a modified ACRpedi30 response is often used with the addition of absence of systemic features. Inactive disease is defined as a disease state with no active arthritis, no systemic features, no uveitis, normal ESR and physician's global assessment indicating no disease activity.[123]

Statistical analyses

Relative risk (RR) and corresponding 95% CI were calculated for each trial independently. An appropriate statistical method for conducting adjusted indirect treatment comparisons is the Bucher method.[121] Because in the present study each comparison consisted of two trials (one trial vs the other), random-effects meta-analysis and meta-regression were not applicable. In the Bucher method, the relative efficacy of two treatments (A and B) versus a common control group (C) are compared according to the following formula: $LnRR'AB=LnRR_{AC}-LnRR_{BC}$ (where

LnRR=natural logarithm of the risk ratio). The underlying similarity assumption of the Bucher method dictates that trials may differ on study and patient characteristics not related to the treatment outcome, but, if these characteristics are modifiers of the relative treatment effects, then the estimates of the indirect comparisons are biased. To ensure that the same relative effects of a certain drug could have been expected across included trials in the indirect comparisons, indirect comparisons were conducted only between clinical trials with the same design (withdrawal trial with an open-label lead-in phase vs parallel RCTs), and with inclusion of approximately the same patient group with regard to disease duration at baseline and JIA categories included. The results of the adjusted indirect comparisons are given as RR with 95% CIs. Two-sided p values of <0.05 were considered significant. Analyses were performed with Stata V.12. For data structure and statistical code in Stata, see online supplementary text. We report outcomes according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices.[124 125] See online supplementary table S1 for the PRISMA Checklist.

RESULTS

A total of 17 citations (including citations of congress abstracts and slides of oral presentation) describing 11 different trials were included. Design and patients' characteristics of the included trials are described in table 1 (for a detailed description, see online supplementary tables S2 and S3). Four withdrawal trials and seven 'classic' RCTs with a parallel study design were included. Overall, eight of the 11 trials met the primary end point in favour of the biological agent. The primary outcome was not met by the infliximab trial, TREAT trial and rilonacept trial.[77 126 127] On the basis of the design and quality of the trials and the characteristics of the patients included, two networks for indirect comparisons were selected, and these are presented in figure 2. Three of the four withdrawal trials (the trials evaluating etanercept, adalimumab and abatacept) included patients with resistant polyarticular course JIA and were compared indirectly (network 1). Polyarticular course JIA (or JRA) was defined in all trials as JIA with five or more active joints at any time during the disease course, and also included patients with systemic arthritis with a polyarticular course. For the details of the categories included, see online supplementary table S2. The fourth withdrawal trial evaluated tocilizumab in only patients with systemic JIA, and 50% of these patients did not have a polyarticular course. In addition, the outcome measure of maintaining a modified ACRpedi30 was different from the other three withdrawal trials. This trial could therefore not be included in the indirect comparison analysis.

Table 1 Description of included studies (for detailed description see online supplementary Table S2 and S3)

Author (acronym)	Year published	Comparison	Study design	Selected out-come	Treatment duration (until evaluation outcome)
Lovell[19]	2000	Etanercept vs placebo	Withdrawal trial†	Disease flare	4 months
Ruperto[127]	2007	Infliximab vs placebo	Randomised placebo-controlled trial	ACRpedi30	14 weeks
Lovell[41]	2008	Adalimumab vs placebo (stratification according to MTX use)	Withdrawal trial†	Disease flare	32 weeks
Ruperto[128]	2008	Abatacept vs placebo	Withdrawal trial†	Disease flare	6 months
Yokota[129 130]	2008	Tocilizumab vs placebo	Withdrawal trial‡	Maintenance of ACRpedi30 response	12 weeks
Ruperto[131]	2011	Canakinumab vs placebo	Randomised placebo-controlled trial	Modified ACRpedi30 response§	15 days
Quartier (ANAJIS)[132]	2010	Anakinra vs placebo	Randomised placebo-controlled trial	Modified ACRpedi30 response§	1 month
De Benedetti (TENDER)[133-137]	2010–2011	Tocilizumab vs placebo	Randomised placebo-controlled trial	Modified ACRpedi30 response§	12 weeks
Lovell[126]	2011	Rilonacept vs placebo	Randomised placebo-controlled trial	Modified ACRpedi30 response§	1 month
Tynjala (ACUTE-JIA)[78 138]	2011	Infliximab+ MTX vs MTX	Randomised open-label trial	Inactive disease	54 weeks
Wallace (TREAT)[77]	2012	Etanercept+ tapered prednisone +MTX vs placebo +MTX	Randomised placebo-controlled trial	Inactive disease	6 months

*Number of patients included in randomised phase.

†Only ACRpedi30 responders included in double-blind phase.

‡Only ACRpedi30 responders with CRP<5mg/l were included in double-blind phase.

§Modified ACRpedi30 response varied between ACRpedi30 response plus absence of fever, and an ACRpedi30 response together with no fever over the past 8 days and 50% decrease or normalisation of both ESR and CRP levels.

	Included JIA/ JRA categories	No. of patients*	Systemic JIA included (%)	Mean disease duration (years)	Previous biologic use (%)	JADAD score for quality
	Polyarticular course JRA	51	33	5.8	0	4
	Polyarticular course JRA	122	16	3.9	0	4
	Polyarticular course JRA	133	?	3.8	0	4
	Polyarticular course JIA	122	19	3.9	17	5
	Systemic JIA	43	100	4.7	?	5
	Systemic JIA	84	100	3.4	?	3¶
	Systemic JIA	24	100	3.7	54	4
	Systemic JIA	112	100	5.2	?	3¶
	Systemic JIA	24	100	3.1	29 (prior anakinra use)	2¶
	Early polyarticular course JIA	60	0	0.16	0	2
	Early polyarticular course JIA (RF pos and neg categories only)	85	0	0.42	0	3

¶Assessment of quality of trial not complete because of insufficient information available (congress abstracts only).

ACRpedi30 response=American College of Rheumatology paediatric 30 response; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; JIA=juvenile idiopathic arthritis; JRA=juvenile rheumatoid arthritis; MTX=methotrexate; neg=negative; pos=positive; RF=rheumatoid factor.

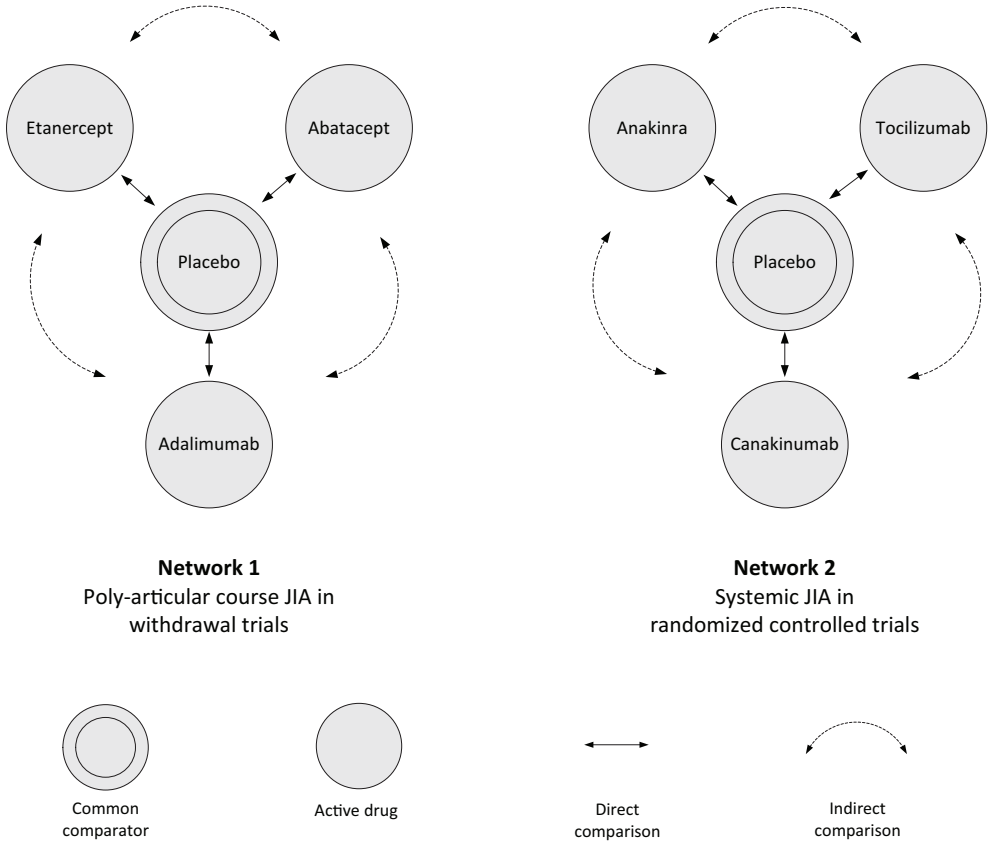

Figure 2 Network diagrams of selected indirect comparisons. JIA=juvenile idiopathic arthritis. Access the article online to view this figure in colour.

Of the seven randomised controlled parallel trials, four only included patients with systemic JIA. These trials compared anakinra, tocilizumab, canakinumab and rilonacept with placebo. No detailed efficacy data of the double-blind phase in the rilonacept trial was given, and rilonacept could therefore not be included in this indirect comparison analysis (network 2). The RCT evaluating infliximab by Ruperto *et al*[127] included patients with polyarticular course JIA and could not be included in either network 1 (withdrawal trials) or network 2 (systemic JIA). Finally, two RCTs included patients with early JIA (after mean disease duration of 0.16–0.42 year). However, because of significant differences in the inclusion of rheumatoid factor positive patients (36% vs 2%), no valid indirect comparisons could be made.[77 138]

Network 1. Withdrawal trials in poly-articular course JIA

For the three comparable withdrawal trials, the disease duration at baseline varied between 3.8 and 5.8 years, and the mean baseline age was between 10.6 and 12.3 years. The percentage of patients with systemic JIA with polyarthritis in the adalimumab withdrawal trial was unclear. Inclusion of systemic JIA varied between the etanercept and abatacept trials (33% and 19% patients with systemic JIA, respectively), but inclusion of rheumatoid factor positive patients was similar across all three trials (21–24%). Seventeen per cent of patients who were previously non-responsive to TNF-α antagonists were included in the abatacept trial compared with none in the etanercept and adalimumab trials. Of the patients who started treatment in the open-label lead-in phase, 64–78% entered the double-blind phase. Baseline disease characteristics of the patients included in the double-blind phase with regard to number of joints with arthritis, physician's assessment of disease activity, and CHAQ scores were comparable between the three trials. Indirect comparisons indicated no differences in efficacy between these three drugs (table 2).

Network 2. Randomized placebo-controlled parallel trials in systemic JIA

The three selected randomised placebo-controlled parallel trials compared anakinra, tocilizumab and canakinumab with placebo. The duration of the double-blind phase was 12 weeks for the tocilizumab trial, 1 month for the anakinra trial, and 15 days for the canakinumab trial. The inclusion criteria with regard to disease duration and non-response to oral corticosteroids were similar. Indirect comparisons identified no significant differences between the drugs with regard to the achievement of a modified ACRpedi30 response (table 2).

Table 2 Outcomes of trials and indirect comparisons

Author	Comparison	Outcome	Patients included (n)	Patients with outcome active drug arm (n/N)	Patients with outcome control arm (n/N)	RR (95% CI) for outcome
Network 1						
Lovell *et al*[19]	Etanercept vs placebo	Disease flare	51	7/25	21/26	0.35 (0.18 to 0.67)
Lovell *et al*[41]	Adalimumab (combined)* vs placebo	Disease flare	133	27/68	44/65	0.59 (0.42 to 0.82)
	Adalimumab (no MTX) vs placebo	Disease flare	58	13/30	20/28	0.61 (0.38 to 0.97)
	Adalimumab (plus MTX) vs placebo	Disease flare	75	14/38	24/37	0.57 (0.35 to 0.92)
Ruperto *et al*[128]	Abatacept vs placebo	Disease flare	122	12/60	33/62	0.38 (0.22 to 0.66)
Network 2						
Quartier *et al*[132]	Anakinra vs Placebo	Modified ACRpedi30 response†	24	8/12	1/12	8.00 (1.17 to 54.50)
De Benedetti *et al*[133] [135-137]	Tocilizumab vs Placebo	Modified ACRpedi30 response†	112	64/75	9/37	3.51 (1.97 to 6.24)
Ruperto *et al*[131]	Canakinumab vs Placebo	Modified ACRpedi30 response†	84	36/43	4/41	8.58 (3.35 to 21.97)

Indirect Comparison	RR (95% CI)	p Value
Network 1	Disease flare	
Etanercept vs adalimumab (combined)*	0.59 (0.28 to 1.24)	0.16
Etanercept vs adalimumab (no MTX)	0.57 (0.25 to 1.28)	0.17
Etanercept vs adalimumab (plus MTX)	0.61 (0.27 to 1.38)	0.23
Etanercept vs abatacept	0.92 (0.39 to 2.18)	0.85
Adalimumab (combined)* vs abatacept	1.56 (0.81 to 2.99)	0.18

Adalimumab (no MTX) vs abatacept	1.61 (0.78 to 3.33)	0.20
Adalimumab (plus MTX) vs abatacept	1.51 (0.72 to 3.13)	0.27
Adalimumab (no MTX) vs adalimumab (plus MTX)	1.07 (0.55 to 2.09)	0.85
Network 2	**Modified ACRpedi30 response**†	
Anakinra vs tocilizumab	2.28 (0.31 to 16.93)	0.42
Anakinra vs canakinumab	0.93 (0.11 to 7.91)	0.95
Tocilizumab vs canakinumab	0.41 (0.14 to 1.23)	0.11

*The stratified methotrexate arms combined.

†Modified ACRpedi30 response was defined in the anakinra trial as an ACRpedi30 response together with no fever over the past 8 days and 50% decrease or normalisation of both erythrocyte sedimentation rate and C-reactive protein levels, and in the tocilizumab and canakinumab trials as an ACRpedi30 response together with no fever.

ACRpedi30 response=American College of Rheumatology paediatric 30 response; RR=relative risk; MTX=methotrexate.

DISCUSSION

In this systematic review, we found that, in JIA, 11 trials compared biological agents with placebo or sDMARDs, and no trials compared biological agents directly. Because these trials differed with regard to design and patient characteristics, not all trials could be included in the indirect comparisons. Two networks of similar trials were identified in order to make valid indirect comparisons. For polyarticular course JIA, etanercept, adalimumab and abatacept seem equally efficacious in preventing disease flare after response to treatment. Canakinumab, tocilizumab and anakinra seem to produce comparable improvement in systemic JIA.

To the best of our knowledge, this is the first attempt to indirectly compare the efficacy of biological agents in JIA. The results of indirect comparisons in RA are not conclusive, but generally seem to indicate that TNF inhibitors are more effective than anakinra, and etanercept is more effective than other TNF inhibitors.[103 118 139] Tocilizumab seems to be more effective in RA than TNF inhibitors and abatacept.[117 140] In the present study, anakinra and tocilizumab were only investigated in systemic JIA.

Indirect comparisons of etanercept, adalimumab and abatacept in network 1 did not identify significant differences in efficacy. However, no definite conclusions could be drawn because of the differences in case mix and design of the trials. In addition, small differences were not likely to be detected because of the small number of patients included in the trials. Some of the characteristics of the patients in the etanercept trial may be associated with poorer outcome. The mean disease duration before the start of biological treatment

was longer (5.8 years in the etanercept trial vs 3.8 and 3.9 years in the adalimumab and abatacept trials, respectively) and the proportion of patients with systemic JIA was higher (33% in the etanercept trial vs 19% in the abatacept trial). In contrast, in the abatacept trial, 17% of the patients were previously non-responders to TNF inhibitors, indicating a more therapy-resistant group.

With regard to trial design, the observed treatment duration in the etanercept trial (4 months) was shorter than in the adalimumab and abatacept trials (8 and 6 months, respectively). Because shorter trial duration means that there is a smaller chance of reaching the time-dependent outcome (disease flare), shorter treatment duration may result in better outcomes. On the other hand, the elimination time for etanercept ($t_{1/2}$ 70 h) is shorter than that for adalimumab and abatacept (both $t_{1/2}$ ~2 weeks), which might counteract the differences in trial duration. Owing to these differences, the estimate of comparative efficacy may be biased. An important conclusion from the comparisons in this network is that trials that are highly comparable with regard to design and case mix are needed in paediatric rheumatology.

Because these results could not be compared with similar analyses or with head-to-head trials including patients with JIA, the only feasible comparison is with data from observational studies performed in JIA. Extensive observational data on etanercept for polyarticular course JIA are available, all showing impressive effects both short and long term.[29 46] Observational studies analysing adalimumab and abatacept in polyarticular course JIA are scarce.[102 141] Adalimumab seems to be mainly preferred when uveitis is present.[42] A small number of observational studies did compare the effectiveness of etanercept with that of infliximab in polyarticular course JIA. No differences in effectiveness were found; however, because of the chimeric structure of infliximab and the associated immunogenicity, infliximab was discontinued more often.[142-144] Unfortunately, an indirect comparison between etanercept and infliximab could not be performed because of trial design dissimilarities. Parallel trials in the second network were highly comparable, and the indirect comparisons found anakinra, canakinumab and tocilizumab to be equally effective for systemic JIA. Unfortunately, no trials have investigated TNF inhibitors in systemic JIA only, and therefore the relative effect of TNF inhibitors compared with IL-1 and IL-6 blockers in systemic JIA could not be evaluated. Observational studies do indicate that etanercept is effective in some patients with systemic JIA.[29 40 49] Many studies have found anakinra to be highly effective,[145 146] but observational studies that evaluate canakinumab and tocilizumab in systemic JIA are still lacking.

Until conclusive differences are established, the choice of biological agent for JIA should

mainly depend on drug availability, safety, practical reasons (such as interval of injections) and treatment costs. Further, more insight into features other than clinical characteristics, such as cytokine and genetic profiling, may contribute to this decision making. Focus could be shifted from treatment of the heterogeneous group of all JIA categories to tailored patient-specific care.

A recent review indicated that the National Institute for Health and Clinical Excellence prefers direct comparisons in decision making. Even in the absence of direct comparisons, key decisions are based on information from original trials, rather than available indirect comparisons.[147] Head-to-head trials are still required, but, until conclusive direct evidence is established, decisions will have to be based on existing sources. In contrast with observational studies and meta-analyses, the indirect treatment comparison method allows the opportunity to preserve the strengths of randomisation. Thereby it is less likely that any differences between treatments observed through indirect comparisons are due to differences between patients that are unrelated to treatment effect.

The internal validity of indirect treatment comparison is highly dependent on (i) appropriate identification of studies, (ii) quality and internal validity of the included trials, and (iii) fulfilment of the similarity assumption.[148 149] We identified all studies systematically, and, to minimise publication bias, checked trial registers; no additional trials that were completed could be identified. To our knowledge, all performed trials were identified. Trial quality was assessed, but varied greatly. Unfortunately, not all trials could be fully assessed, because data had to be extracted from conference abstracts.[150] Bias may have been introduced, because these abstracts were not part of peer-reviewed publications. Earlier trials for registration commissioned by pharmaceutical industries gained the best scores, while more recent trials that evaluated treatment strategies for approved biological agents performed worst. The inferior trial quality of the TREAT trial was one of the reasons for excluding this trial from the indirect comparison. It is very likely that patients in the prednisone arm will develop signs of Cushing's syndrome, leading to unavoidable unblinding issues. The results of the withdrawal trials, although of high quality, should be placed in a different context. Instead of an estimation of the initial response to the treatment, the effect of treatment discontinuation has been researched. Better protection of flares after the primary response does not necessarily imply better initial treatment responses. It should be noted that, although the Jadad criteria assessed the most important aspects of quality of trial design, this does not guarantee that the trial was conducted perfectly.

The biggest challenge for this indirect comparison was fulfilling the similarity assumption, because of the heterogeneity of the disease and the scarcity of trials. Relying on clinical

judgement, six trials were found to be suitable for indirect comparisons. The two networks consisted of methodologically identical trials with inclusion of patients with approximately the same disease duration and JIA categories, which were thought to be the most important confounders.[29 151] Although classification criteria for juvenile arthritis differed between withdrawal trials (JRA and JIA), patients included were identical with regard to number of joints with arthritis.

Nevertheless, the included trials were not perfectly identical. Treatment duration varied between trials and is likely to have influenced the measured outcome. Furthermore, although the similarities predominated, differences between the withdrawal trials included co-medication used and previous treatment of some patients with biological agents. Because of the small number of trials and the limited number of patients included, it was unfeasible to further adjust our results using meta-regression, subgroup analysis or sensitivity analysis.

In conclusion, this review provides a comprehensive overview of the conducted trials that evaluated biological agents for treatment of JIA. Taking into account the differences between trials, this is the first study to carefully conclude that the short-term efficacy of etanercept, adalimumab and abatacept seems similar for polyarticular course JIA, and that of anakinra, canakinumab and tocilizumab seems similar for systemic JIA. Because of the observed differences between trials, more comparable trials and head-to-head trials directly comparing biological agents are urgently needed. For now, the paediatric rheumatologist must rely on these indirect comparisons, supplemented by observational data derived from cohort studies and safety, practical and financial arguments.

ONLINE SUPPLEMENTARY TEXT: SEARCH STRATEGY

PubMed, hits: 308

(arthritis, juvenile rheumatoid[MeSH] OR (arthrit*[tiab] AND (juvenil*[tiab] OR childhood[tw] OR child[tw] OR children[tw]))AND (Biologic Agents[mesh] OR antirheumat*[tw] OR Biologic*[tiab] OR Tumor Necrosis Factors[mesh] OR Tumor Necrosis Factor*[tiab] OR Tumour Necrosis Factor*[tiab] OR TNFR-Fc fusion protein[tw] OR etanercept[tw] OR adalimumab[tw] OR infliximab[tw] OR abatacept[tw] OR interleukin 1*[tw] OR anakinra[tw] OR interleukin 6*[tw] OR tocilizumab[tw] OR canakinumab[tw] OR certolizumab[tw] OR golimumab[tw] OR rituximab[tw] OR rilonacept[tw]) AND (randomized controlled trial[152] OR controlled clinical trial[152] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mesh] NOT humans[mesh])

Embase, hits: 316

('juvenile rheumatoid arthritis'/de OR ((juvenile* OR child*) NEAR/3 arthrit*):ab,ti) AND ('antirheumatic agent '/exp OR (antirheumat* OR Biologic* OR (('Tumor Necrosis' OR 'Tumour Necrosis') NEXT/1 Factor*) OR 'TNFR-Fc fusion protein' OR etanercept OR adalimumab OR infliximab OR abatacept OR 'interleukin 1' OR 'interleukin 6' OR anakinra OR tocilizumab OR canakinumab OR certolizumab OR golimumab OR rituximab OR rilonacept):de,ab,ti) AND (random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEXT/1 over*):ab,ti OR placebo*:ab,ti OR ((doubl* OR singl*) NEXT/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'crossover procedure'/de OR 'double-blind procedure'/de OR 'randomized controlled trial'/de OR 'single-blind procedure'/de) NOT ([animals]/lim NOT [humans]/lim)

Cochrane, hits: 61

(arthrit* AND (juvenil* OR childhood OR child OR children)) AND (Biologic Agents OR antirheumat* OR Biologic* OR Tumor Necrosis Factor* OR Tumour Necrosis Factor* OR TNFR-Fc fusion protein OR etanercept OR adalimumab OR infliximab OR abatacept OR interleukin 1* OR anakinra OR interleukin 6* OR tocilizumab OR canakinumab OR certolizumab OR golimumab OR rituximab OR rilonacept

ONLINE SUPPLEMENTARY TEXT: DATA STRUCTURE AND STATISTICAL CODE (STATA)

control =placebo
event_c =number of events in placebo group
noevent_c =number of patients without a event in placebo group
sample_c =total number of observations in the placebo group
event_t =number of events in treatment group
noevent_t =number of patients without a event in treatment group
sample_t =total number of observations in the treatment group
compb =comparison A vs B=1; A vs C =0

* Indirect comparison using the Bucher method:

I: meta-analysis of trials of BvA (compb equal to 1)
metan event_t noevent_t event_c noevent_c if compb==1, rr randomi nograph
local logrr1=log($S_1)
local se1=$S_2
display `logrr1'
display `se1'

II: meta-analysis of trials of CvA (compb equal to 0)
metan event_t noevent_t event_c noevent_c if compb==0, rr randomi nograph
local logrr2=log($S_1)
local se2=$S_2
display `logrr2'
display `se2'

III: computation of log RR, RR and se for indirect comparison
local logrr_aic=`logrr1'-`logrr2'
display `logrr_aic'
local rr_aic=exp(`logrr_aic')
display `rr_aic'
local se_aic=sqrt(`se1'^2+`se2'^2)
display `se_aic'

IV: computation of confidence intervals, z-value and P-value

```
local ll_aic=exp(`logrr_aic'-(1.96*`se_aic'))
display `ll_aic'
local ul_aic=exp(`logrr_aic'+(1.96*`se_aic'))
display `ul_aic'

local z_aic=`logrr_aic'/`se_aic'
display `z_aic'
if `z_aic'>0 local p_aic=2*(1-normal(`z_aic'))
if `z_aic'<=0 local p_aic=2*normal(`z_aic')
display `p_aic'
```

ONLINE SUPPLEMENTARY TEXT: TABLE S2 DESCRIPTION OF INCLUDED STUDIES

	Etanercept (Lovell)	**Infliximab (Ruperto)**	**Adalimumab (Lovell)**	**Abatacept (Ruperto)**	**Tocilizumab (Yokota)**
Acronym	-	-	-	-	-
Year published	2000	2007	2008	2008	2008
Inclusion criteria*	Aged 4-17 years, JIA with presence of at least 5 swollen joints and at least 3 joints with limitation of motion and pain, tenderness or both, and inactive to NSAIDs and MTX at least 10mg/m^2/ week	Aged 4-18 years, JIA with presence of at least 5 swollen joints and suboptimal response to MTX >=3 months	Aged 4-17 years, JIA with presence of at least 5 swollen joints and at least 3 joints with limitation of motion, and not responded adequately to NSAIDs and patients either not previously treated with MTX or irresponsive/ intolerant to MTX	Aged 6-17 years, JIA with presence of at least 5 swollen joints, or in absence of swelling, with limited range of motion, and inadequate response to, or intolerance to, at least 1 DMARD (including biologic agents)	Aged 2-19 years, active systemic JIA, inadequate response to oral corticosteroids > 3 months
Exclusion criteria†	Previously treated with other biologics	Previously treated with any TNF-alpha antagonist, presence of active systemic symptoms or active uveitis	Previously treated with other biologics or recently treated with IV-IG, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids (IA, IM or IV).	Active uveitis, active systemic symptoms	Development of MAS during pre-study hospital admission
Design	Randomized double-blind placebo-controlled withdrawal trial 3 months open-label lead-in phase (all received drug), only ACRpedi30 responders included in 4 month double-blind phase	Randomized double-blind placebo-controlled trial first 14 weeks placebo-controlled, than comparison of 2 dosing regimens	Randomized double-blind placebo-controlled withdrawal trial 16 weeks open-label lead-in phase (all received drug), only ACRpedi30 responders in 32 week double-blind phase. Stratification for MTX use	Randomized double-blind placebo-controlled withdrawal trial 4 months open-label lead-in phase (all received drug), only ACRpedi30 responders in 6 month double-blind phase included.	Randomized double-blind placebo-controlled withdrawal trial 6 weeks open-label lead-in phase (all received drug), only those ACRpedi30 responders with CRP <5mg/L in 12 week double-blind phase
Medication	1) Etanercept 0.4mg/ kg (max 25mg) twice weekly; 2) placebo	1) Infliximab (3mg/kg) + MTX during 52 wks; 2) placebo infusions + MTX first 14 wks and then infliximab (6 mg/ kg) + MTX MTX: 10-15mg/ m2/wk oral or IM	1)Adalimumab 24mg/ m2 (max 40mg) every other week; 2) placebo For those in MTX stratum: stable doses of at least 10mg/m2/ wk.	1) Abatacept 10mg/kg (max 1000mg); 2) placebo	1) Tocilizumab 8mg/kg every 2 weeks; 2) placebo

	Anakinra (Quartier)	Canakinumab (Ruperto)	Tocilizumab (DeBenedetti)	Rilonacept (Lovell)	Infliximab (Tynjala)	Etanercept (Wallace)
	ANAJIS-trial	-	TENDER	-	ACUTE-JIA	TREAT
	2010	2009 (congress abstract only)	2010-2011 (congress abstracts only)	2011 (congress abstract only)	2011	2012
	Aged 2-20 years, active** systemic JIA despite oral corticosteroids (>=0.3mg/day or 10mg/ day, whichever was less), more than 6 months disease duration and presence of active systemic disease	Aged 2-19 years, systemic JIA with active systemic features	Aged 2-17 years, active systemic JIA, disease duration >6 months and inadequate response to previous NSAIDs and corticosteroids	Aged 5-20 years, active systemic JIA with fever and/or rash	Aged 4-15 years, JIA with presence of at least 5 swollen joints and 3 joints with pain or tenderness and limitation of motion, and with arthritis for at least 6 weeks, but no longer than 6 months	Aged 2-17 years, poly-articular JIA (RF positive or RF negative and patients without psoriasis but with a first-degree relative with psoriasis) of less than 12 months duration
	Previously treated with IL-1 inhibitor	Unknown	Unknown	Unknown	Systemic JIA and ever use of DMARDs and/or steroids	Patients with past or current uveitis. Previously treated with other biologics and DMARDs other than MTX
	Randomized double-blind placebo-controlled trial first month placebo-controlled phase, than open-label treatment period with all patients receiving anakinra	Randomized double-blind placebo-controlled trial 4-week placebo-controlled phase, than open-label treatment period with all patients receiving canakinumab	Randomized double-blind placebo-controlled trial 12-weeks placebo-controlled phase (randomization 2:1) with a rescue phase after 2 weeks with standard of care therapy, than open-label treatment period	Randomized double-blind placebo-controlled trial 4-week placebo-controlled phase, than open-label treatment period with all patients receiving rilonacept	Randomized open-label treatment strategy trial 54 week open-label trial comparing 3 treatment arms: 1) infliximab + MTX, 2) MTX only, and 3) COMBO (MTX + SSZ + plaquenil)	Randomized double-blind placebo-controlled treatment strategy trial 12 month trial comparing: 1) MTX + Etanercept + tapered PRED, and 2) MTX + placebo etanercept + PLAC prednisone
	1) Anakinra 2 mg/kg/ day (max 100mg/day); 2) placebo	1)Canakinumab (single dose, 4mg/kg, max 300mg) 2) Placebo	1) Tocilizumab 8mg/kg for patients ≥30kg and 12mg/kg for patients <30kg; 2) placebo	1) Rilonacept (2.2mg/ kw/ week, max 160mg); 2) Rilonacept (4.4mg/ kw/ week, max 320mg); 3) placebo	1) Infliximab (3-5 mg/ kg) +MTX; 2) MTX only; 3) SSZ (40mg/ kg/ day up to 2000mg/ day) +plaquenil (5mg/ kg/ day up to 300mg/ day)+MTX MTX:15mg/m2/wk, max25mg	1) MTX (0.5mg/ kg/wk, max 40mg s.c.)+Etanercept (0.8mg/ kg/week, max 50mg)+PRED (0.5mg/ kg/day, max 60mg, tapered to 0 by 17 wks); 2) MTX+plac

	Etanercept (Lovell)	Infliximab (Ruperto)	Adalimumab (Lovell)	Abatacept (Ruperto)	Tocilizumab (Yokota)
Co-medication regimens	MTX needed to be discontinued at least 14 days and other DMARDs and IA steroids 28 days before receipt etanercept. Stable doses of NSAIDs, low doses of steroids (≤0.2 mg/kg/day, max 10 mg) and pain medications (except during the 12 hours before a joint assessment) were permitted during trial.	DMARDs other than MTX and IA steroids not permitted within 4 weeks prior to study entry and during trial. Low-dose steroids (<0.2mg/kg/day or 10mg/day, whichever was less), 1 NSAID, 1 analgesic not NSAID, folic acids and narcotic or opoid analgestics permitted during trial.	Stable doses of NSAIDs and low dose corticosteroids (≤0.2 mg/kg/day, max 10 mg) and pain medications (except during the 12 hours before a joint assessment) permitted.	All DMARDs (including biologics, but excluding MTX) and IA steroids needed to be discontinued at least 4 weeks before receipt abatacept and were prohibited during trial. MTX at stable dose and NSAIDs/analgesics and folic acids were allowed. Oral corticosteroids were stabilised 4 weeks before enrollment (at 10mg/day or 0.2 mg/kg, whichever was less).	IA steroids, methyl-prednisone pulse, immunosuppressive drugs and DMARDs not allowed for 2 weeks before receipt study drug. TNF-blockers not allowed for 12 weeks before receipt study drug. Doses of oral corticosteroids had to be stable for 2 weeks prior study entry. During the study only stable doses of oral steroids were allowed.
Primary endpoint	Disease flare‡	ACRpedi30	Disease flare‡	Time to disease flare‡	Maintenance of ACRpedi30 response and CRP<15mg/L
Secondary endpoints (open-label extension file excluded)	ACRpedi 30/50/70 at 7 months	ACRpedi50/70	ACRpedi 30/50/70/90/100	% of patients with disease flare‡, ACRpedi30/50/70/90 responses	ACRpedi30/50/70 Systemic feature score
JADAD score	Score: 4 Randomly assigned, but sequence of randomization not discussed (+1). Double-blind, placebo also injection (+2). Withdrawals described (+1)	Score: 4 Randomly assigned, but sequence of randomization not discussed (+1). Double-blind, placebo also injection (+2). Withdrawals described (+1)	Score: 4 Randomly assigned, but sequence of randomization not discussed (+1). Double-blind, placebo also injection (+2). Withdrawals described (+1)	Score: 5 Randomly assigned, and computer generated (+2). Double-blind, placebo also injection (+2). Withdrawals described (+1)	Score: 5 Randomly assigned, dynamic allocation (+2). Double-blind, placebo also injection (+2). Withdrawals described (+1)

* For all trials: patients had to have normal or nearly normal platelet, white-cell, and neutrophil counts, hepatic aminotransferase levels, and results of renal function test. Only the differences in inclusion criteria between trials are given in the table.

† For all trials: exclusion of pregnant and lactating patients and patients with major concurrent medical conditions (including serious infection, tuberculosis, malignancy). Girls with child-bearing potential were required to use contraception throughout the study. Only the differences in exclusion criteria between trials are given in the table.

** Active defined as at least 3 of the following criteria: 1) physicians' global >=20/100, 2) parent/patient assessment of wellbeing >=20/100, 3) CHAQ>=0.375/3.0, 4) >=2 joints with arthritis, 5) >=2 joints with non-reversible limited range of motion, and 6) ESR>30mm/h.

‡ ACRpedi30 for a flare, defined as worsening of 30% or more in 3 of the 6 response variables, and improvement of 30%

	Anakinra (Quartier)	Canakinumab (Ruperto)	Tocilizumab (DeBenedetti)	Rilonacept (Lovell)	Infliximab (Tynjala)	Etanercept (Wallace)
	IV or IA steroids, immunosuppressive drugs and DMARDs had to be stopped at least 1 month before study entry. No immunosuppressive drugs or DMARDs allowed during trial. Doses of NSAIDs and corticosteroids had to remain stable 1 month before and during double blind phase.	Unknown	Stable dose of MTX and NSAIDs continued. Tapering of oral corticosteroids was allowed at weeks 6 and 8 for patients who met the ACRpedi70 criteria plus ESR<20mm/h plus no fever	Unknown	IA steroids and NSAIDs permitted during trial Escape regimen: if after 12 weeks of treatment no ACRpedi75 then MTX dose doubled.	MTX (<=0.5mg/ kg/ week, max 40mg) started no longer than 6 weeks prior to enrolment and up to 2 IA steroid injections at least 2 weeks before baseline and oral prednisone up to 4 weeks before baseline allowed. During the study use of 1 NSAID and folium acid and up to 2 IA steroid infections were allowed.
	Modified ACRpedi30***	Modified ACRpedi30***	Modified ACRpedi30***	Modified ACRpedi30***	ACRpedi75	Inactive disease after 6 months
	ACRpedi 30 Modified ACRpedi50/70	Unknown	ACRpedi50/70/90	Unknown	Inactive disease, duration inactive disease, drug survival ACRpedi30/50/ 70/90/100	ACRpedi70 after 4 months
	Score: 4 Randomly assigned, computer generated random list (+2). Double-blind, placebo not described, (injection?) (+1). Withdrawals described (+1)	Score: 3 Randomly assigned, but sequence of randomization not discussed (+1). Double-blind, placebo not described, (injection?) (+1). Withdrawals described (+1)	Score: 3 Randomly assigned, but sequence of randomization not discussed (+1). Double-blind, placebo not described, (injection?) (+1). Withdrawals described (+1)	Score: 2 Randomly assigned, but sequence of randomization not discussed (+1). Double-blind, placebo not described, (injection?) (+1). Withdrawals not described (0)	Score: 2 Randomly assigned, but sequence not described (+1). Not double-blind (0). Withdrawals described (+1)	Score: 3 Randomly assigned, and computer generated (+2). Double-blind, however placebo for prednisone (max 60mg) must have let to unblinding issues because of the presence or absence of cushing's syndrome (0). Withdrawals described (+1)

or more in no more than one variable (changes from values at time of randomization). Added criterion in the etanercept trial: minimum of 2 joints with arthritis, and, if global assessments used to defined a flare, a minimal change of 20mm (on a 0-100mm scale). Added criterion in the adalimumab trial: if the number of active or limited joints were used to define a flare, at least 2 joints had to have arthritis or limited motion respectively. In the adalimumab trial no minimum increase for the global assessments was given. Ruperto et al. did not add a minimum joint count (active or limited), but, if global assessments were used to define a flare, a minimal change of 20mm (on a 0-100mm scale) needed to be present.

*** Modified ACRpedi30 response was defined in anakinra (Quartier) trial as an ACRpedi30 response together with no fever over the past 8 days and 50% decrease or normalization of both ESR and CRP levels, in the Ruperto, De Benedetti and Lovell trial as an ACRpedi30 response together with no fever.

[SSZ= sulfasalazine; LOCF= last observation carried forward; IM= intra-muscular, IA= intra-articular, IV= intra-venous]

ONLINE SUPPLEMENTARY TEXT: TABLE S[3] PATIENT POPULATION INCLUDED AND REPORTED EFFICACY

	Etanercept (Lovell)	Infliximab (Ruperto)	Adalimumab (Lovell)	Abatacept (Ruperto)	Tocilizumab (Yokota)
N included in open-label phase	69	-	171	190	56
N entering double-blind part	51 (74%)	122 (100%) (efficacy analysis for 117 patients)*	144 (84%) eligible for double blind part, 133 (78%) entered	122 (64%)	43 (77%)
Baseline patient and disease characteristics (of patients in double blind part only)					
Female	34 (67%)	102 (84%)	103 (77%)	88 (72%)	28 (65%)
Mean age (years)	10·6	11·2	11·3	12·3	8·7
Mean disease duration (years)	5.8	3.9	3.8	3.9	4.7
JIA category					
Oligo-articular extended	3 (6%)	28 (23%)	?	16 (13%)	-
Oligo-articular persistent	-	-	?	2 (2%)	-
Poly-articular RF pos or neg	31 (61%)	74 (61%)	?	80 (66%)	-
Systemic	17 (33%)	19 (16%)	?	23 (19%)	43 (100%)
Unknown (numbers do not add)	-	1 (1%)	-	1 (1%)	-
Positive for RF	12 (24%)	27 (22%)	28 (21%)	26 (21%)	0 (0%)
Previous MTX	51 (100%)	122 (100%)	87 (65%)	At least 94 (77%)	?
Previous Biologic	0 (0%)	0 (0%)	0 (0%)	21 (17%)	?
Disease characteristics at baseline (of patients in double blind part only †)					
Mean no. active joints	29**	19	17	16	4**
Mean no. limited joints	7**	18	14	16	0**
Mean physicians' global (0-100)	65**	51	59	53	51**
Mean global assessment of wellbeing (0-100)	50**	43	48	41	53**
Mean CHAQ score (0-3)	1.4**	1.2	1.1	1.2	0.7**
Mean ESR mm/hour	34**	33	?	31	37**
Efficacy (double blind part only)					
Duration placebo-controlled part	4 months	14 weeks	32 weeks	6 months	12 weeks
Disease flare (%)	DRUG: 28% PLAC: 81%	-	Plus MTX: DRUG: 37% PLAC: 65% No MTX: DRUG: 43% PLAC: 71%	DRUG: 12 (20%) PLAC: 33 (53%)	-
Median time to flare	DRUG: >116 days PLAC: 28 days	-	-	DRUG: insufficient events PLAC: 6 months	-
Maintenance of ACRpedi30 and CRP <5mg/L	-	-	-	-	DRUG: 80% PLAC: 17%
Modified ACRpedi30***	-	-	-	-	-

	Anakinra (Quartier)	Canakinumab (Ruperto)	Tocilizumab (DeBenedetti)	Rilonacept (Lovell)	ACUTE-JIA (Tynjala)	TREAT (Wallace)
	-	-	-	-	-	-
	24 (100%)	84 (100%)	112 (100%)	24 (100%)	60 (100%) (efficacy analysis for 59 patients)*	85 (100%)
	15 (63%)	?	?	16 (67%)	38 (63%)	72 (85%)
	8·5	?	?	12·6	9·6	10·5
	3.7	3.4	5.2	3.1	0.16	0.42
	-	-	-	-	?	?
	-	-	-	-	-	-
	-	-	-	-	?	?
	24 (100%)	84 (100%)	122 (100%)	24 (100%)	-	-
	-	-	-	-	-	-
	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	31 (36%)
	19 (79%)	?	?	?	0 (0%)	10 (12%)
	13 (54%)	?	?	7 (29%, anakinra use)	0 (0%)	0 (0%)
	16	14	20	11	18	22
	17	?	?	7	10	15
	60	?	?	55	55	71
	52	?	?	60	30	54
	1.6	?	?	1.5	0.8	1.2
	50	?	?	?	36	37
	1 month	15 days	12 weeks	4 weeks	54 weeks	4 months/ 6months‡
	-	-	-	-	-	-
	-	-	-	-	-	-
	-	-	-	-	-	-
	DRUG: 67% PLAC: 8%	DRUG: 84% PLAC: 10%	DRUG: 85% PLAC: 24%	? (numbers unknown)	-	-

	Etanercept (Lovell)	Infliximab (Ruperto)	Adalimumab (Lovell)	Abatacept (Ruperto)	Tocilizumab (Yokota)
Efficacy (double blind part only)					
Duration placebo-controlled part	4 months	14 weeks	32 weeks	6 months	12 weeks
ACRpedi30	-	DRUG: 63.8% PLAC: 49.2%	-	-	-
ACRpedi50	-	DRUG: 50.0% PLAC: 33.9%	-	-	-
ACRpedi70	-	DRUG: 22.4% PLAC: 11.9%	-	-	-
ACRpedi75	-	-	-	-	-
ACRpedi90	-	-	-	-	-
Inactive disease	-	-	-	-	-

* In Infliximab trial 5 patients excluded from efficacy analysis: missing data of 3 patients in PLAC-group (1 withdrew consent, 2 patients potential unblinding issues) and of 2 patients in DRUG group (both potential unblinding issues). In anakinra trial 1 patient excluded from efficacy analysis because of protocol violation

† For Adalimumab (Lovell et al.) trial disease characteristics of all patients included in open-label phase (MTX group n=85, no MTX n=86) are given, because values for patients entering double-blind phase only were not reported.

** Median given instead of mean

‡ ACRpedi70 score after 4 months, inactive disease after 6 months of double-blind period

*** Modified ACRpedi30 response was defined in Quartier trial as an ACRpedi30 response together with no fever over the past 8 days and 50% decrease or normalization of both ESR and CRP levels and in the Lovell, De Benedetti and Ruperto trial as an ACRpedi30 response together with no fever

	Anakinra (Quartier)	Canakinumab (Ruperto)	Tocilizumab (DeBenedetti)	Rilonacept (Lovell)	ACUTE-JIA (Tynjala)	TREAT (Wallace)
	1 month	15 days	12 weeks	4 weeks	54 weeks	4 months/ 6months ‡
	DRUG: 92% PLAC: 58%	-	-	-	TNF: 100% COMBO: 85% MTX only: 60%	-
	-	-	DRUG: 85% PLAC: 11%	-	TNF: 100% COMBO: 80% MTX only: 60%	-
	-	-	DRUG: 71% PLAC: 8%	-	TNF: 100% COMBO: 70% MTX only: 60%	MTX+ETN+ PRED: 71% MTX+PLAC: 44%
	-	-	-	-	TNF: 100% COMBO: 65% MTX only: 50%	-
	-	-	DRUG: 37% PLAC: 5%	-	TNF: 84% COMBO: 60% MTX only: 45%	-
	-	-	-	-	TNF: 68% COMBO: 40% MTX only: 25%	MTX+ETN+ PRED: 40% MTX+PLAC: 23%

Chapter 3.4 **Switching to other biologic agents after failing etanercept**

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ABSTRACT

Objective. To evaluate the effectiveness and safety of switching to a second or third biological agent in juvenile idiopathic arthritis (JIA) after etanercept failure.

Methods. The Arthritis and Biologicals in Children Register aims to include all Dutch JIA patients who have used biological agents. Data on the disease course were used to estimate drug survival with Kaplan–Meier and calculate adverse event (AE) rates.

Results. Of 307 biologically naive JIA patients who started etanercept, 80 (26%) switched to a second and 22 (7%) to a third biological agent. During 1030 patient-years of follow-up after the introduction of etanercept, 49 switches to adalimumab, 28 infliximab, 17 anakinra, four abatacept and four trial drugs were evaluated. 84% (95% CI 80% to 88%) of patients who started etanercept as a first biological agent were, after 12 months, still on the drug, compared with 47% (95% CI 35% to 60%) who started a second and 51% (95% CI 26% to 76%) who started a third biological agent. Patients who switched because of primary ineffectiveness continued the second agent less often (32%, 95% CI 12% to 53%). After etanercept failure, drug continuation of adalimumab was similar to infliximab for patients with non-systemic JIA; anakinra was superior to a second TNF-blocker for systemic JIA. AE rates within first 12 months after initiation were comparable for each course and each biological agent.

Conclusions. Switching to another biological agent is common, especially for systemic JIA patients. A second (and third) agent was less effective than the first. The choice of second biological agent by the physician mainly depends on availability and JIA category.

INTRODUCTION

The introduction of etanercept has much improved outcomes in juvenile idiopathic arthritis (JIA) patients. However, despite this treatment success in most patients, approximately 10–22% of previously biologically naive JIA patients discontinue etanercept within 12 months because of a lack of effectiveness or intolerance.[29 144 153] Different biological agents targeting different cytokines are now available. Tumour necrosis factor alpha (TNFα) antagonists are the most often prescribed biological agents for JIA patients. Etanercept (approved since 2000), adalimumab (approved since 2008) and infliximab (not approved for JIA, but used off-label) all antagonise TNFα, but have different mechanisms of action.[154 155] Therefore treating physicians consider a switch to a second TNFα antagonist after failing the first. Besides these TNFα antagonists, abatacept (a selective T-cell costimulation modulator) has been approved in 2010 for JIA patients who have failed at least one synthetic disease-modifying antirheumatic drug and a TNFα blocker. For systemic JIA, blocking interleukin (IL)-1 and IL-6 cytokines seems to be of greater value and targeting these cytokines (tocilizumab (approved for systemic JIA since 2011) and anakinra and canakinumab (not approved for JIA, but used off-label)) appears promising.[129 132 146 156 157]
Besides a few case series,[101 158-160] only one larger observational study regarding switching between TNFα blocking agents in JIA has been published up to now.[144] That retrospective chart review from Tynjala *et al*[144] mainly described patients switching from etanercept to infliximab (and vice versa) and concluded that a switch to a second anti-TNFα agent was a reasonable option. Studies focusing on switching from etanercept to agents targeting other cytokines are lacking for JIA; however, some do include patients with a history of TNF-blocking agents. On the basis of mainly case series combined with expert opinion, the American College of Rheumatology (ACR) recommended equally in 2011 a second TNFα inhibitor or abatacept for polyarticular JIA patients who failed the first TNFα inhibitor. For the systemic category with active arthritis they recommended a switch from anakinra to etanercept, or vice versa, or a switch to abatacept.[161] As evidence with regard to switching in JIA is scarce, we evaluated the effectiveness and safety of switching to other biological agents after failing etanercept during a long follow-up period.

PATIENTS AND METHODS

Study design and subjects

This study was part of a multicentre prospective observational register; the Arthritis and

Biologicals in Children (ABC) Register. This register aims to include all Dutch JIA patients who use or previously used biological agents since the introduction of etanercept in 1999. The study protocol was approved by the Medical Ethics Committee at Erasmus MC Rotterdam and by all participating hospitals. The treating physicians collected and entered patient and disease characteristics in the web-based register at baseline, followed after 3 months of treatment, after 15 months and yearly thereafter.[22] These data included the variables of the JIA disease activity score (ie, the JIA core set): physician's global assessment of disease activity on a visual analogue scale (VAS; range 0–100 mm, 0 best score), the childhood health assessment questionnaire (CHAQ; range 0–3, 0 best score) by patients/parents, including global assessment of wellbeing by a VAS, number of active and limited joints and erythrocyte sedimentation rate (ESR).

In addition to the follow-up outcome data entered at 3 months and yearly thereafter, extra data entry times were at the time of any important events, such as stopping or switching biological agents and adverse events (AE).

For this study we selected all JIA patients who started etanercept as a first biological agent before 1 January 2010, to allow for sufficient follow-up. The reported switches were restricted to the introduction of a second and third biological agent. Switches to trial drugs were mentioned; however, the outcomes of patients switching to trials had to be excluded from the analyses. Reasons for switching were based on the clinicians' opinion and classified into: lack of effectiveness, intolerance/AE, uveitis and other reasons. Lack of effectiveness was subsequently categorised in primary non-response or partial response depending on whether patients had achieved an ACRpedi50 response at least once during follow-up exposed to etanercept or the second biological agent. An ACRpedi50 response has been defined as at least 50% improvement in three or more variables of the JIA core set and a worsening of no more than one variable by more than 30%.[44]

Effectiveness

As a proxy for effectiveness of treatment, drug adherence until discontinuation due to ineffectiveness of treatment, AE or non-compliance was estimated with Kaplan–Meier. Patients were censored when discontinuation because of disease remission occurred, or when still receiving the drug at the time of last study visit.

Furthermore, inactive disease was analysed only for those patients who switched to another biological agent because of lack of effectiveness (primary non-response and partial response) of etanercept on arthritis. Inactive disease was defined, according to a modified definition of Wallace with a physician's global assessment of disease activity indicating no

disease activity defined as a score of 10 mm or less, on a scale of 0–100 mm.[45]

Safety

All medically important infectious and non-infectious AE and all serious adverse events (SAE, defined according to the US Food and Drug Administration) were documented. Flaring of JIA was not considered as an AE but as an outcome of treatment response. We calculated the overall AE rates (including SAE) and the SAE rates per patient-year within the first year after initiation of a biological agent, accounting for possible discontinuation of the biological agent. We limited our safety analyses to the first year after initiation of the biological agent, because the follow-up durations differed between the observed biological agents and AE rates are reported to be higher within the first year. We considered infections that recurred within a patient as separate AE, but non-infectious AE that recurred were counted only once.

Statistical analysis

The multiple imputation method of the AregImpute function of the R statistical package was applied to impute missing values of the JIA core sets at observed follow-up moments. Only when at least three of the six JIA core set variables were present were the remaining values of the core sets imputed.

For patients who switched from etanercept to a second and from a second to a third biological agent with lack of effectiveness as the reported reason (n=58 to a second and n=15 to a third agent), ACRpedi50 scores were calculated in order to categorise these patients as primary non-responder or partial responder. Five per cent of the JIA core set variables were missing at the start of etanercept (median of 0 missing variables per core set; IQR 0–0) and 34% at the start of the second agent (median of two missing variables per core set; IQR 2–4). A total of 244 follow-up visits was recorded, of which 128 visits were used in order to categorise these patients. Missing during these follow-up visits were: 26% of the variables and a median of 0.5 missing variables per core set (IQR 0–2.5).

Of all patients who switched to the second agent because of lack of effectiveness, inactive disease was calculated at the fixed follow-up visits after 3 and 15 months of treatment. Forty-six of the 58 patients had a 3-month follow-up visit and 24% (11 of 46) of the ESR values, 7% (three of 46) of the reported active joint counts and 44% (20 of 46) of the physician's global assessments for disease activity were missing. Forty-three patients had a follow-up visit 15 months after switch, and 37% of the ESR values, 33% of the reported active joint counts and 65% of the physician's global assessments for disease activity were missing.

Descriptive statistics were reported as absolute frequencies, or as median values with an IQR. Depending on the tested baseline variable, Mann–Whitney U tests and χ^2 test were used to perform comparisons between patients who switched and patients who never switched. In addition, a logistic regression was performed to adjust the associated factors for follow-up duration since the start of etanercept, which was thought to be an important confounder. Another logistic regression was performed to identify the association between the reason to discontinue a second agent and the reason to switch from a first to a second biological agent. Results of the logistic regression models are presented as OR with 95% CI, and p values were calculated using the Wald's test.

Differences in drug continuation (according to Kaplan–Meier) were defined by the log-rank test when comparing two groups and by the log-rank Mantel–Cox when comparing multiple groups. All reported p values were based on two-sided tests for significance, and p values less than 0.05 were considered statistically significant. SPSS V.17.0.1 and R statistical package 2.10.1 were used for the analyses.

RESULTS

Of the 307 JIA patients included, 80 (26%) switched to a second and 22 (7%) to a third biological agent. A flow chart of switching patterns is given in figure 1. Patient and disease characteristics are listed in table 1. Median follow-up duration since the start of the second biological agent was 18 months (IQR 7–38), and since the start of the third 14 months (IQR 6–35). Adjusted for follow-up duration, patients who switched to a second biological agent were more likely to have the systemic category, had shorter disease duration before the start of etanercept and were younger at the start of the first biological agent, and at the start of etanercept had higher CHAQ scores. Reasons for a switch to a second or third biological agent are reported in table 2. Lack of effectiveness of treatment was the most frequently reported reason for both switches.

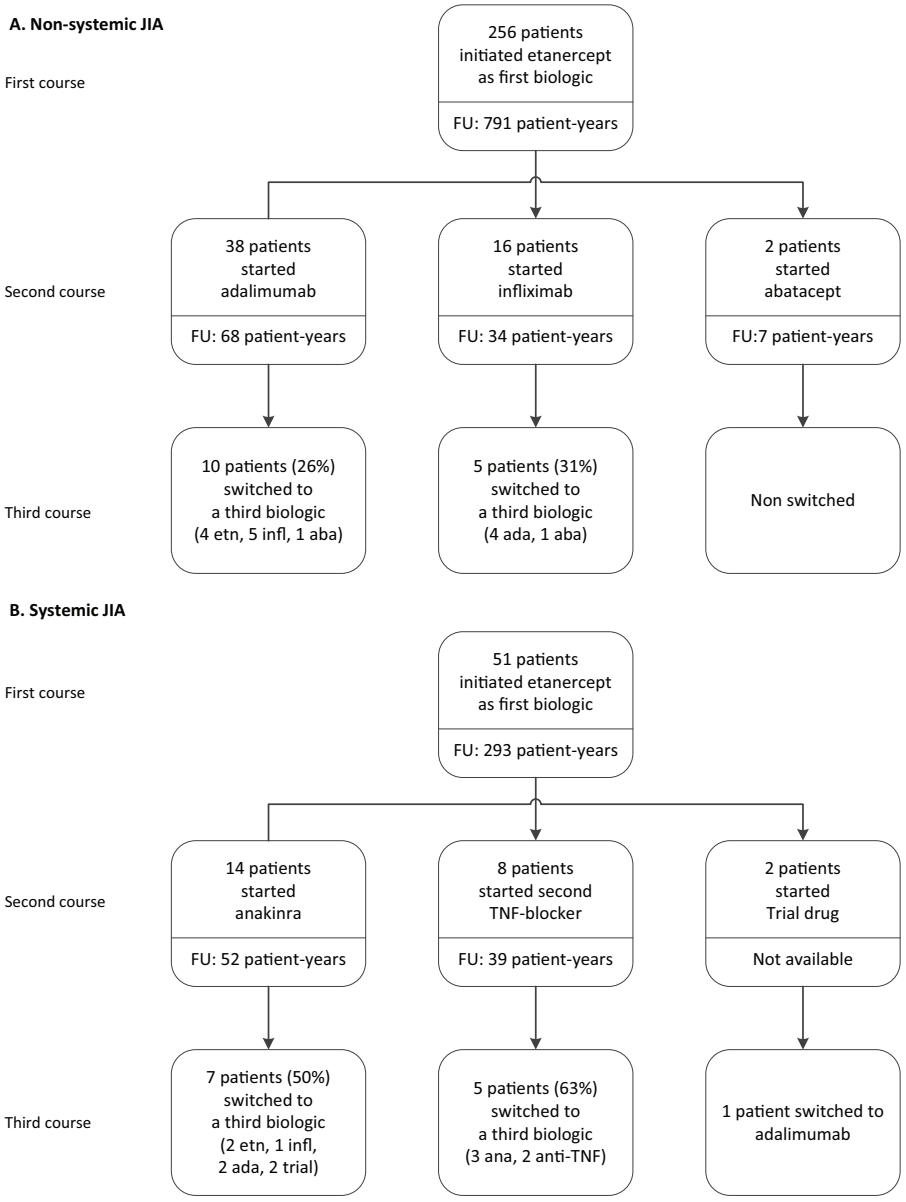


Figure 1 (A, B) Flow-chart of switching between biological agents recorded in the Arthritis and Biologicals in Children Register. The recorded follow-up duration (patient-years) since start or switch are reported below that specific start or switch (eg, 68 patient-years of follow-up were recorded since switch to adalimumab in non-systemic juvenile idiopathic arthritis patients). aba=abatacept; ada=adalimumab; ana=anakinra; etn=etanercept; FU=follow-up; infl=infliximab.

Table 1 Patient and disease characteristics before start etanercept

	JIA patients who never switched (n=227)	Switchers to a second agent (n=80)†	Switchers to a third agent (n=22)†
Female	155 (68)	56 (70)	17 (77)
Age at onset JIA (years)	8.0 (3.9-11.4)	5.1 (2.9-11.8)	4.1 (2.9-10.9)
Disease duration before start etanercept (years)**	3.2 (1.5-6.7)	2.1 (1.0-4.3)	1.4 (0.9-2.8)
Age at start etanercept (years)**	13.0 (9.7-15.5)	10.2 (6.2-13.8)	8.2 (5.0-12.3)
Duration follow-up since start of etanercept (months)*	29.4 (16.3-51.3)	41.8 (25.6-69.2)	57.1 (35.1-94.1)
Category JIA			
Systemic-onset JIA**	27 (12)	24 (30)	11 (50)
Polyarticular JIA RF negative	92 (41)	30 (38)	5 (23)
Polyarticular JIA RF positive	24 (11)	5 (6)	3 (14)
Oligoarticular JIA persistent	9 (4)	1 (1)	0 (0)
Oligoarticular JIA extended	45 (20)	16 (20)	3 (14)
Arthritis psoriatica	17 (8)	2 (3)	0 (0)
Enthesitis-related arthritis	13 (6)	2 (3)	0 (0)
Medication history before etanercept			
Systemic glucocorticoids	104 (46)	50 (63)	17 (77)
Methotrexate	202 (89)	70 (88)	19 (86)
Other synthetic DMARD	92 (41)	32 (40)	6 (27)
Disease activity at start etanercept			
VAS physician	62 (47-72)	60 (37-75)	62 (37-79)
CHAQ score**	1.4 (0.9-2.0)	1.9 (1.2-2.4)	2.1 (1.6-2.6)
VAS pain patient/parent	57 (25-75)	60 (34-78)	74 (52-83)
VAS wellbeing patient/parent	50 (27-74)	58 (35-79)	70 (50-92)
No of joints with arthritis	8 (5-16)	10 (7-17)	11 (9-18)
No of joints with limited motion	7 (3-13)	6 (4-12)	7 (4-11)
ESR	18 (9-35)	19 (7-38)	23 (11-55)

Numbers given are: absolute numbers (%) or median (IQR).

*p Value <0.0001 (switchers compared with patients who never switch, Mann-Whitney U test).

**p Value <0.05 adjusted for follow-up duration (switchers compared with patients who never switch, logistic regression analysis, p value based on Wald's test). Because of the non-normal distribution of disease duration before the start of etanercept a logarithmic transformation was used.

†Patients who switched to a third agent are also represented in the switchers to a second agent patient group.

CHAQ=child health assessment questionnaire; DMARD=disease-modifying anti-rheumatic agent; ESR=erythrocyte sedimentation rate; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; VAS=Visual analogue scale.

Table 2 Reasons for switching

	Switch to a second agent (n=80)	Switch to a third agent (n=22)
Ineffectiveness: primary	26 (33)	12 (55)
Partial effect / loss of response	32 (40)	3 (14)
Adverse events / intolerance	11 (14)	5 (23)
Inflammatory Bowel Disease	5	-
Urosepsis	1	-
Chest pain, dyspnoea, air trapping lung	1	-
Injection site reaction / fear of injections	1	4
Other	3	1
Combination ineffectiveness and adverse events	1 (1)	-
Uveitis	8 (10)	1 (5)
Non-compliance	2 (3)	-
Unknown	-	1 (5)

Most patients experienced no treatment pause between the discontinuation of a biological agent and introduction of another biological agent, 17 patients started the second agent after a median biological treatment pause of 8 months (IQR 2–32), and 12 patients started the third agent after a median biological treatment pause of 4 months (IQR 2-22). The biological treatment pause seemed mainly caused by the limited availability of other biological agents during the observed time period and the occurrence of SAE as a reason to discontinue biological treatment.

The drug survival of the first, second and third introduced biological agents is reported in figure 2. Eighty-four per cent (95% CI 80% to 88%) of patients who started etanercept as a first biological agent were, after 12 months, still on the drug, compared with 47% (95% CI 35% to 60%) of patients who started a second biological agent and 51% (95% CI 26% to 76%) of patients who started a third biological agent.

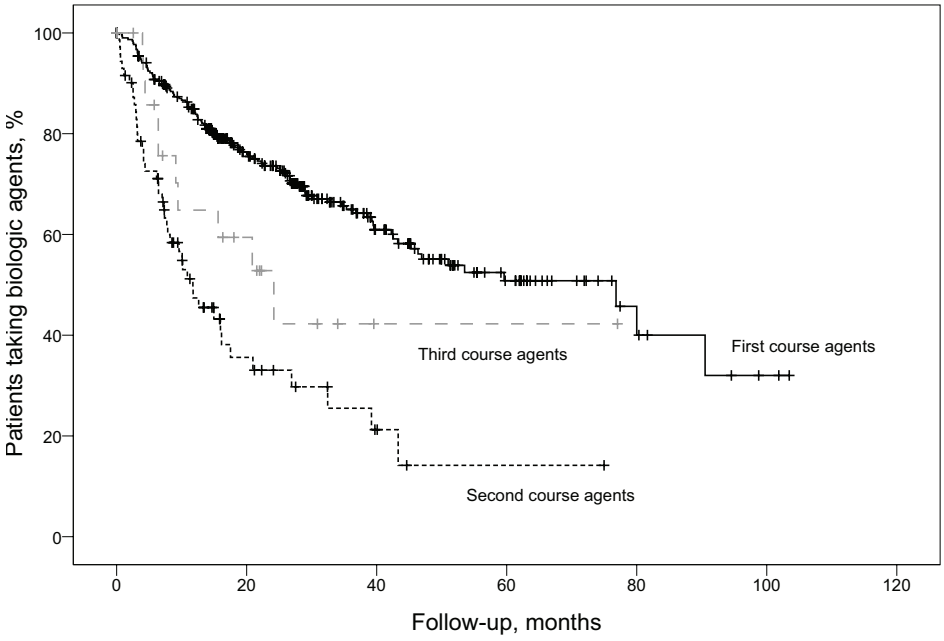


Figure 2. Drug continuation of first, second and third course biologics. Kaplan–Meier estimate of overall drug continuation until discontinuation of the first, second and third introduced biological agent due to ineffectiveness, adverse events or non-compliance. Vertical lines indicate censoring (censoring is defined as the time a patient discontinued etanercept because of disease remission or, when still receiving the drug, the time of last study visit). Log-rank test (Mantel–Cox) compares the overall drug survival differences between the three courses of biological agents.

Table accompanying Figure 2:

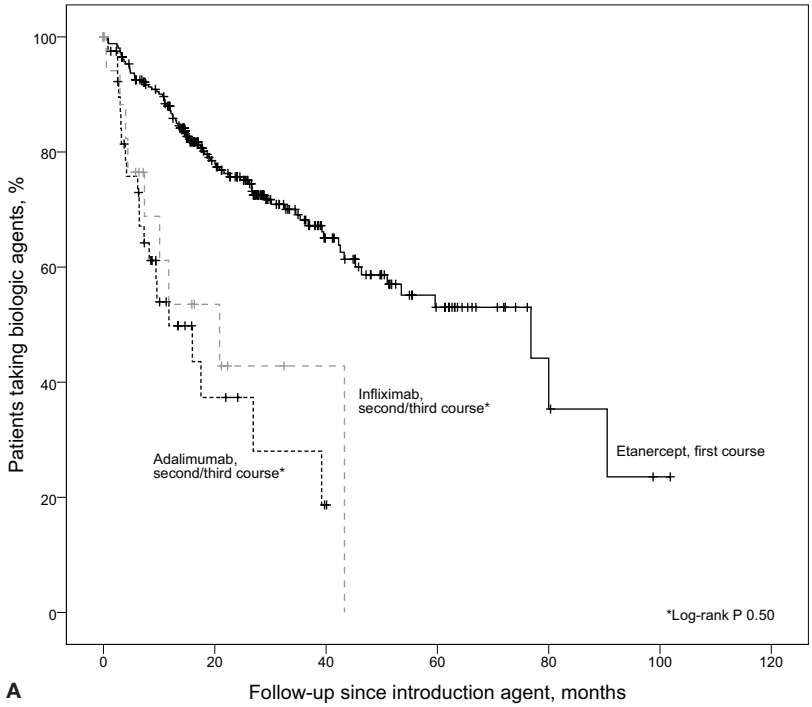
	No of patients	No of patients with events	No of patients censored
First course (etanercept)	307	107	200
Second course	78*	44	34
Third course	19**	9	10

* Two patients who used a trial drug as a second biological agent had to be excluded.

** Two patients who used a trial drug as a third biological agent had to be excluded.

Switching patterns

The majority of patients with non-systemic JIA categories switched between anti-TNFα agents only. These patients discontinued adalimumab because of ineffectiveness or AE in 21 of the 42 times it was started as a second/third biological agent, and infliximab in nine of the 21 times it was started as a second/third biological agent. Drug survival of the adalimumab courses in JIA patients with non-systemic JIA categories (50% on drug after 12 months, 95% CI 32% to 67%) was not different compared with the infliximab courses (54%, 95% CI 28 to 79, log-rank p=0.50,figure 3A). Systemic JIA patients most often started anakinra after etanercept failure (17 times of anakinra as second/third biological agent). All systemic JIA patients who started adalimumab discontinued it due to ineffectiveness or intolerance, six of seven patients (86%) discontinued infliximab and 11 of 17 patients (65%) anakinra. After etanercept failure, systemic JIA patients continued anakinra (65% on drug after 12 months, 95% CI 42 to 87) more often than a second TNFα antagonist (21%, 95% CI 0 to 43, log-rank p=0.006). Drug survival of anakinra as a second/third agent was not different from drug survival of etanercept as a first agent (figure 3B).



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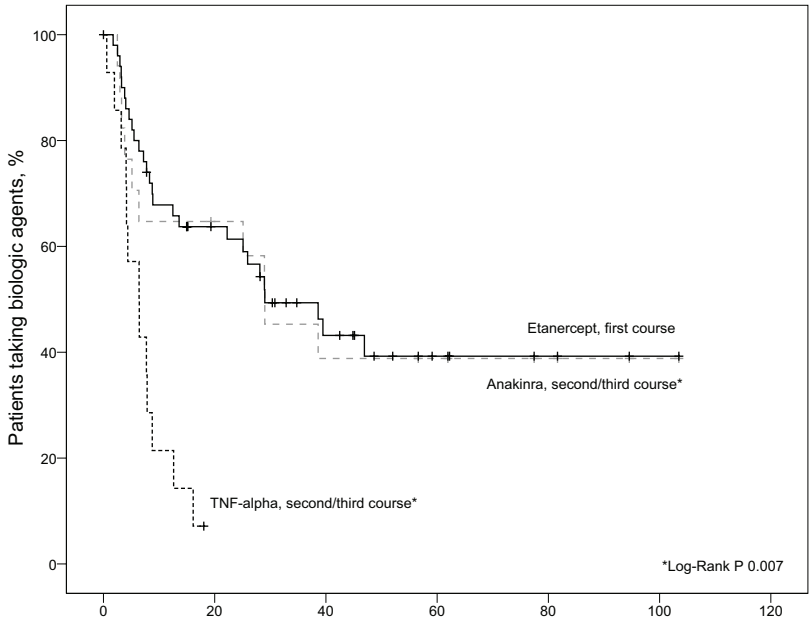

B

Figure 3 Drug continuation of biological agents introduced in systemic juvenile idiopathic arthritis (JIA) and non-systemic JIA categories. Kaplan-Meier estimate of overall drug continuation until discontinuation of the agent due to inefficacy or adverse events. Vertical lines indicate censoring (censoring is defined as the time a patient discontinued etanercept because of disease remission or end of follow-up). (A) Compares the drug survival of etanercept (introduced as the first biological agent) with adalimumab and infliximab as the second/third introduced agents for patients with non-systemic JIA categories. (B) Compares the drug survival of etanercept (introduced as the first biological agent) with anakinra, adalimumab and infliximab as the second/third introduced agents for patients with systemic JIA. Log-rank test compares the drug survival difference between the second/third introduced biological agents (*marked categories).

Table accompanying figure 3

	No of patients	No of patients with events	No of patients censored
Table accompanying Figure 3A			
Etanercept (first)	256	79	177
Adalimumab (second/third)	42	21	21
Infliximab (second/third)	21	9	12
Table accompanying Figure 3B			
Etanercept (first)	51	27	24
Anakinra (second/third)	17	10	7
Adalimumab or infliximab (second/third)	14	13	1

Effectiveness of second biologic on active arthritis

Forty-six of the 58 patients who switched to a second agent due to lack of effectiveness had follow-up data 3 months after switch, for two patients too many variables were missing and two of the remaining 44 patients (5%) achieved inactive disease. Of the 43 patients with 15 months of follow-up, unfortunately for 14 patients too many variables were missing, and five of the remaining 29 patients (17%) achieved inactive disease.

Influence of reason switching

Patients who switched to a second biological agent because of primary non-response to treatment (n=24, two patients excluded because of inclusion in a drug trial) seemed to continue the second agent less often (32% on drug after 12 months, 95% CI 12% to 53%) than patients who switched because of partial response (50% on drug after 12 months, 95% CI 30% to 70%) and the remaining reasons combined (61% on drug after 12 months, 95% CI 38% to 83%).

Discontinuation of a second biological agent because of lack of effectiveness was associated with lack of effectiveness as a reason to switch from the first to the second agent (OR 8.0, 95% CI 1.7 to 37.4), but not with AE as a reason to switch from the first to the second biological agent (OR 0.1, 95% CI 0.0 to 1.1).

Of the eight patients who switched to a second agent because of uveitis, all switched to adalimumab. Median drug survival on adalimumab for these patients was 11.7 months; four patients (50%) discontinued adalimumab (two because of a flare of arthritis, one because of AE and one reason unknown).

Safety of switching

Very few patients switched because of safety issues from etanercept to the second agent (11 of 307 patients) and from the second to the third agent (five of 80 patients). Within 1 year after the start of etanercept as the first biological agent, 0.23 AE/patient-year and 0.01 SAE/patient-year (0.55 AE/patient-year of patients who switched) were reported, and within 1 year after the start of the second biological agent 0.32 AE/patient-year and 0.00 SAE/patient-year, and of the third biological agent 0.36 AE/patient-year and 0.00 SAE/patient-year.

Within the first year, 0.42 AE/patient-year during the 49 adalimumab courses were observed, 0.19 AE/patient-year during the 28 infliximab courses and 0.32 AE/patient-year during the 17 anakinra courses.

DISCUSSION

This prospective observational study addressed the important clinical question paediatric rheumatologists are confronted with: 'What to do after failing etanercept in JIA?'
In this study we show that switching to a second biological agent in JIA occurs frequently in daily practice and seems to be a safe option for JIA patients who fail etanercept. The effectiveness of a second (and third) biological agent is debatable and seems especially low when the first biological agent was discontinued because of primary ineffectiveness.
This is the second observational study on the effectiveness and safety of switching between biological agents in JIA. In the present study, most patients switched from etanercept to adalimumab, while in the study by Tynjala *et al*[144] mainly a switch between etanercept and infliximab was described. We showed that, while JIA patients continued etanercept as a first biological agent more often, 47% of the switchers, who previously did not responded to etanercept, continued their second biological agent after 12 months of treatment. A lower percentage (32%) was seen for patients who discontinued etanercept because of primary ineffectiveness. This drug survival rate of a second biological agent is slightly lower than the 58% reported by Tynjala *et al.*[144] The number of patients who achieved inactive disease 15 months after switch (17%) was substantially lower than the reported 32% in previously biologically naive JIA patients treated with etanercept.[29] In rheumatoid arthritis (RA), a meta-analysis with over 4000 RA patients has been conducted and a drug continuation rate of 61.8% 1 year after the introduction of a second TNFα antagonist of treatment seemed higher than in JIA.[162] In that study the percentage of RA patients achieving inactive disease was not reported, but an ACR70 response was reached in only 14% of patients. While a first biological agent was more effective, switching seems justifiable, because only very limited other therapeutic options are available after biological treatment.
The question remains: 'Which patients should switch and to what type of biological agent?' We have shown that, in daily practice, patients with non-systemic JIA categories mainly switched between TNFα inhibitors only. An important observation was that, for patients with non-systemic JIA categories, no differences between the effectiveness of adalimumab versus infliximab after etanercept failure were seen. Abatacept, even though it has been approved after TNFα failure, was only used in four patients, which is largely influenced by the limited availability of abatacept within the study period. The majority of the patients with systemic JIA switched between etanercept and anakinra. After etanercept failure, anakinra was superior compared with a second TNF-blocker. Anakinra now has a more prominent

place in the treatment of systemic JIA with systemic features and is often the first choice biological agent.[161] Other IL-1 and IL-6 antagonists were, besides prescriptions in the presence of randomised clinical trials, not available during this study period and therefore were not observed in the present study.

Another observation was that patients who switched to a second biological agent with uveitis as the reason, all switched to adalimumab. A study by Simonini *et al*[98] recently showed that adalimumab seems to be more efficacious in maintaining uveitis remission than infliximab. Unfortunately, the evaluation of the effectiveness on uveitis is beyond the scope of our register.

In this study we showed that the AE rates are comparable for each course of biological agents, and are also comparable for each specific biological agent. This is in contrast with data from Curtis *et al,*[161] who showed a higher rate of hospitalised infections in switchers compared with RA patients who did not switch and a higher rate of hospitalised infections with infliximab use compared with the use of other available biological agents. Furthermore, we showed that AE as a reason to switch from a first to a second agent did not influence the chance of discontinuation of the second agent for AE; however, the number of patients with AE was small. Our finding that switching between biological agents in JIA in our study was not associated with an increased safety risk is reassuring.

This prospective observational study has some limitations. Because of the observational study design, reflecting a real-life setting, the choice of treatment is subject to the preferences of the treating physicians. The observed switching patterns are inevitably influenced by the availability of biological agents within the study period. The register started when etanercept became available for the treatment of JIA, and other biological agents were introduced later, which will have had an effect on the treatment choices of physicians. Furthermore, the study period is limited until the patients become 18 years of age. For patients followed for a longer period after the start of etanercept, we had a higher chance to observe a switch. The percentage of switching in this observational study is likely to be underreported. Therefore, together with the low number of patients per introduced biological agent and the uncontrolled nature of an observational study, these indirect comparisons between the different biological agents are difficult and should be interpreted with care.

Furthermore, clinicians are allowed to start or discontinue concomitant medications during the observed periods. The strength of this observational study is a reflection of daily clinical care; however, the lack of evaluation of these concomitant medications should be noted.

The switchers represent a heterogeneous patient group. The presence of systemic features,

uveitis and anti-drug antibodies are all important factors that influence treatment choices of the physicians and could affect treatment responses. In further studies these should all be taken into account to identify the best strategy of switching for each individual patient.
In conclusion, switching from etanercept to a second biological agent occurs frequently in daily practice and, as limited options are available, seems justifiable for JIA patients who fail etanercept. After etanercept failure, adalimumab and infliximab were equally effective in JIA patients with non-systemic JIA categories, while anakinra was superior to a second TNFα blocking agent in systemic JIA. The effectiveness of a second biological agent was lower than the first biological agent and seems especially low when the first agent was discontinued because of primary ineffectiveness. The choice of second biological agent by the physician mainly depends on availability of biological agents and the JIA category.

Chapter 3.5 **Comparing effectiveness of biologic agents for JIA in an observational study design: the challenge of confounding by indication**

Janneke Anink
Mark Lunt
Kimme Hyrich
Lisette W.A. van Suijlekom-Smit

Submitted as:
Janneke Anink, Mark Lunt, Kimme Hyrich, Lisette W.A. van Suijlekom-Smit. Comparing effectiveness of biologic agents for JIA in an observational study design: the challenge of confounding by indication

ABSTRACT

Objective. Although the number of biologic agents available for the treatment of juvenile idiopathic arthritis keeps increasing, few comparative effectiveness studies have been performed. No head-to-head trials are available and indirect comparisons of the trials were limited by lack of comparability. This study attempts to assess comparative effectiveness of adalimumab an etanercept in three ways in an observational study.

Methods. Biologic-naïve patients starting either etanercept (n=304) or adalimumab (n=42) were selected from the Arthritis and Biologicals in Children register, who were included between 2004 and 2013. Comparative effectiveness was assessed in three analyses in the same dataset. A linear regression was fitted for the change in JADAS-10, with treatment as one of the covariates. A cox regression was fitted, also using treatment as a covariate, again using drug persistence as a proxy for treatment effectiveness. Lastly an attempt was made to construct a propensity score for the allocation of treatment, and to apply this propensity score in a logistic regression method with minimal disease activity as outcome measure

Results. In the first two methods, no significant differences were found in effectiveness of the two TNF-inhibitors. The third analysis could not be brought to a successful end, because of the lack of overlap in patient characteristics between the two treatment groups.

Conclusions. The lack of overlap in confounding factors was the most important finding of this study. Physicians interpreting comparative effectiveness and safety studies, but also investigators from other registers and observational studies should be aware of this problem.

INTRODUCTION

In the last decade the treatment of juvenile idiopathic arthritis (JIA) has greatly changed. One of the most important developments was the introduction of biologic treatment. After the approval of the first biologic agent, the TNF inhibitor etanercept in 1999, many new biologic agents followed. These agents also targeted TNF alpha, like adalimumab, or were directed at other cytokines, such as anakinra and tocilizumab. In analogy with developments in the treatment of rheumatoid arthritis (RA) it is to be expected that other agents are to follow, including the biosimilars.[163]

This growth in treatment options implies a more difficult process of choosing one of these drugs. For regulators, patients, parents and physicians to be able to make a well informed choice, data on comparative effectiveness and safety are greatly needed.

For FDA and EMA approval, new drugs need to be tested to prove their short term efficacy and safety in randomized controlled trials (RCTs), in which the active treatment is compared with a placebo. For information on comparative efficacy, ideally two active treatments would be compared directly in a head-to-head (non-inferiority) RCT. However, these trials are not likely to be performed in the future, in part because they would need a large number of biologic-naïve patients, which are not readily available for a rare disease like JIA. The relative effectiveness will therefore have to be studied in different ways, such as observational studies. In this study we will explore the possibility of doing so in the Dutch Arthritis and Biologicals in Children (ABC) register [40], by comparing etanercept and adalimumab, the two approved TNF-alpha inhibitors.

The short term efficacy of these two anti-TNF agents has been established in randomized controlled trials. Observational studies have provided evidence that the two treatments are effective in controlling disease activity in patients with JIA in the long term.[164] Although they both block TNF alpha, there are potential mechanistic differences between the two agents, which may explain why the effectiveness of the drugs differs between diseases (e.g. uveitis, psoriasis, inflammatory bowel disease and arthritis).[18] The difference in effectiveness for arthritis is supported by the observation that many JIA patients that lack response to one, can still be responsive to the other TNF inhibitor.[165] Because the two drugs have a different structure, there is a potential difference in immunogenicity, which may also influence the long term effectiveness of the drug.

Limited information is available on their relative effectiveness. Head-to-head trials were never performed and the indirect comparison of trial data was limited by lack of similarity of the trials and the patients investigated. The indirect comparison did not indicate a

significant difference in efficacy of these two TNF-inhibitors.[166] Based on the available evidence, guidelines for the treatment of JIA make no distinction between the two.[17] Hence, the relative effectiveness of the two TNF inhibitors will have to be studied in observational studies. A drawback of the observational study design is the lack of randomization. This gives rise to the possibility of confounding by indication. In an observational study patient or disease characteristics are able to influence the doctor's choice for prescribing one or the other biologic. These same characteristics may also effect the treatment response. For example, a physician might be more inclined to prescribe adalimumab to a patient with a higher chance to develop uveitis, e.g. a patient with the oligoarticular JIA category. Additionally, having oligoarticular JIA might be associated with the response of the arthritis to the biologic treatment. In a previous study we found that patients in the register who were treated with adalimumab differed from patients who were treated with etanercept.[83] To try to get round these distorting effects, the present study made an attempt to compare the effectiveness of the two treatments, applying various methods to control for confounding by indication.

METHODS

Patients

Patients were retrieved from the Dutch Arthritis and Biologicals in Children (ABC) Register, a multicenter prospective cohort study that aimed to include all Dutch patients initiating biologic treatment.[40] The ABC register contains prospectively obtained data since the introduction of etanercept for JIA in 1999. For the purpose of this study we selected biologic-naïve patients starting either etanercept or adalimumab included in the register between 2004 and 2013. Etanercept was available from 1999 in the Netherlands, for adalimumab this was the case from the end of 2008. In the early years patients with longstanding severe disease were included, who were less comparable to the more recently included patients, therefore patients from 2004 onwards were used for this analysis. To include a patient sample with the highest possible homogeneity with regard to patients characteristics in both treatment groups, we also included patients from the period before 2008, although adalimumab was not yet readily available. This provided us with patients who would have been treated with adalimumab, had it been available, but who were treated with etanercept, because it was the only approved biologic treatment for polyarticular course JIA. JIA patients without active arthritis initiating biologics to treat uveitis only were not included in the analyses, nor were patients participating in treatment strategy trials.

Additionally we excluded patients with systemic JIA, because no patients with this category were treated with adalimumab and therefore no match could be found within this subgroup of patients.

Data collection

In the ABC register, patient and disease characteristics were collected at baseline. Thereafter, data on disease activity by means of the JIA core set is collected after 3 months of treatment and every following year. The variables of the JIA disease activity core set are the physician's global assessment (PGA) of disease activity by visual analogue scale (VAS) (range 0-100 mm, 0 best score), Childhood Health Assessment Questionnaire (CHAQ) (range 0-3, 0 best score) by patients/parents, including global assessment of wellbeing by VAS, number of active and limited joints and erythrocyte sedimentation rate (ESR). Additionally pain is assessed by the patient/parent through VAS. Based on the variables of the JIA core set the juvenile arthritis disease activity score (JADAS-10) was calculated.[23] Change in JADAS-10 within 4 months after start of treatment was the outcome of interest in the second analysis. In the first analysis the outcome of interest was the achievement of minimal disease activity (MDA).[167] MDA is defined as a PGA of 25 or less and no active joints for patients with an oligoarticular course of the disease; for patients with a polyarticular course it is defined as a PGA of 34 or less, a global assessment of wellbeing by the patient of 21 and 1 or no active joints. To apply this definition, our patients were divided in those with oligoarticular and those with polyarticular course JIA. Because the full course of the disease before start of the biologic agent was not known for all patients, we assigned the labels polyarticular and oligoarticular based on the number of active joints at start of etanercept.

Missing data handling

At baseline 8.1% of the JIA core set variables (including VAS pain) were missing. At follow-up 24.6% of the core set variables were missing. Missing data were handled using the chained equations multiple imputation command *ice* in Stata. Ten imputed datasets were created. Adalimumab and etanercept patients were imputed together, because the adalimumab-treated group was too small to be imputed separately. Thus we assumed that the variables that were imputed were related in the same way in both groups.

Statistical analysis

The first approach was a linear regression model of the change in JADAS-10 on possible

confounders which was constructed in etanercept patients. Subsequently we applied this model in the adalimumab patients. Thereby we predicted what the response in change in JADAS-10 would have been, would these patients have been treated with etanercept, and compared these predicted values with the observed change in JADAS-10. Potential confounders were identified beforehand based on pre-existing knowledge of their relationship with the assignment of treatment (either adalimumab or etanercept) and the response to treatment (baseline CHAQ score, disease duration at start of biologic).[29 75 76 83] Other baseline variables considered as possible confounders were PGA, number of previously used DMARDs, ANA status, number of active joints, number of limited joints, global assessment of wellbeing by the patient (VAS), ESR, gender, history of uveitis, JIA category (divided in the two categories oligo-articular and polyarticular) and age at onset.
Secondly, a cox regression analysis was performed to estimate hazard ratios (HRs) for the discontinuation due to ineffectiveness or adverse events. The covariates in this model were the same as those included in the linear regression model, plus the covariate for biologic treatment. Because in this study we included patients from a period before adalimumab was widely available, we added year of inclusion as a covariate.
The third approach we used was a propensity score weighted logistic regression analysis with the outcome variable MDA. The same confounders were considered as in the other models. Propensity scores were constructed using the *prop_sel* method in Stata (developed by Mark Lunt at the University of Manchester, can be freely downloaded). Standardized differences and the expected bias of each confounder were calculated. The expected bias is the likely bias on the treatment effect that an existing imbalance of the confounders in the propensity estimate will cause. A maximum bias of 5% in either direction was considered acceptable in the construction of the propensity score model.
Descriptive statistics are presented as absolute values, mean and SD or as median and IQR whenever appropriate. When medians were reported based on multiply imputed datasets, the average of the medians of all ten sets was taken. All analyses were conducted using Stata/SE version 12.0 and IBM SPSS Statistics 21.

RESULTS

Between 2004 and 2013 304 non-systemic JIA patients started etanercept and 42 patients started adalimumab. Patient and disease characteristics at baseline are described in table 1.

Table 1 Patient and disease characteristics of patients treated with etanercept and adalimumab

Baseline characteristics	Etanercept (n=304)	Adalimumab (n=42)
Year of start biologic treatment, median (IQR)	2008 (2007-2010)	2011 (2010-2012)
Female, n (%)	210 (69)	28 (67)
Age at onset JIA in years, median (IQR)	8.5 (3.5-12.0)	8.4 (2.3-12.2)
Age at start first biological in years, median (IQR)	12.7 (9.3-15.4)	13.0 (8.8-15.8)
JIA disease duration before start biological in years, median (IQR)	2.6 (1.4-5.7)	3.0 (0.8-6.4)
ANA positivity, n (%) (n=302/n=41)	105 (35)	22 (54)
History of uveitis, n (%)	12 (4)	21 (50)
Category JIA, n (%)		
Polyarticular RF negative	129 (42)	7 (17)
Polyarticular RF positive	38 (13)	1 (2)
Oligoarticular extended	76 (25)	8 (19)
Oligoarticular persistent	16 (5)	8 (19)
Psoriatic arthritis	23 (8)	6 (14)
Enthesitis related arthritis	21 (7)	10 (24)
Undifferentiated	1 (0.3)	2 (5)
Number of previously used DMARDs (including MTX), median (IQR)	1 (1-2)	1 (1-2)
Previous use of corticosteroids, n (%)	109 (36)	15 (36)
Disease activity parameters at baseline, median (IQR)		
PGA (0-100) (n=283/n=30)	57 (40-70)	40 (30-60)
CHAQ total (0-3) (n=273/n=28)	1.3 (0.8-2.0)	0.8 (0.3-1.5)
VAS pain (0-100) (n=271/n=28)	59 (30-75)	50 (21-65)
VAS patient (0-100) (n=273/n=28)	55 (29-75)	46 (24-65)
Active joints (n=304/n=42)	7 (4-9)	4 (2-6)
Limited joints (n=289/n=38)	4 (2-9)	3 (2-5)
ESR (n=299/n=39)	13 (7-29)	11 (5-24)
JADAS-10 (0-40), median (IQR) (n=256/n=24)	19 (14-23)	14 (10-17)

IQR=interquartile range; JIA=juvenile idiopathic arthritis; ANA=anti-nuclear antibodies; RF=rheumatoid factor; DMARDs=disease modifying anti-rheumatic drugs; MTX=methotrexate; PGA=global assessment of disease activity by the physician; CHAQ=childhood health assessment questionnaire; VAS=visual analogue scale; ESR=erythrocyte sedimentation rate; JADAS=juvenile arthritis disease activity score

Patients treated with adalimumab differed from patients treated with etanercept. The biggest differences were found in ANA status, history of uveitis and the distribution of the

JIA categories. Adalimumab-treated patients had more often a positive ANA, a history of uveitis, persistent oligoarticular, psoriatic and enthesitis related arthritis. Overall, their disease activity was lower than the disease activity of etanercept-treated patients.

Linear regression approach - observed vs expected

To observe whether etanercept treatment would have been as successful as adalimumab treatment in the adalimumab-treated patients, a linear regression model for change in JADAS-10 adjusted for all prespecified confounders was fitted on the etanercept patients and applied to the adalimumab treated patients. The beta estimates for this multivariate model are displayed in Table 2. JADAS10 was significantly more likely to decrease when a patient had polyarticular JIA (which was to be expected, given that the joint count can decrease more when a patient has polyarticular course JIA than when a patient has oligoarticular disease). For analogous reasons, also the baseline components of JADAS-10 were significant predictors, except for the number of active joints. The estimated beta for the presence of a history of uveitis was large, however the effect was not significant, possibly because there were so little patients with a history of uveitis in the etanercept-treated patient group.

Table 2 Multivariate linear regression for change in JADAS-10 in etanercept-treated patients

Variable	Beta	95% confidence interval	p-value
Male gender	0.58	-0.96 to 2.12	0.46
Age at onset of JIA, years	0.01	0-0.17 to 0.19	0.88
Disease duration, years	-0.16	-0.39 to 0.08	0.20
ANA positive	0.15	-1.35 to1.64	0.85
History of uveitis	-2.45	-5.94 to 1.04	0.17
Previous use of corticosteroids	-1.08	-2.50 to 0.35	0.14
Number of previously used DMARDs	0.91	-0.15 to 1.96	0.09
Polyarticular course JIA	-4.19	-6.18 to -2.20	<0.001
PGA	-0.07	-0.11 to -0.02	0.002
CHAQ	0.66	-0.53 to 1.85	0.27
VAS patient	-0.08	-0.11 to -0.05	<0.001
Number of active joints	0.07	-0.05 to 0.19	0.23
Number of limited joints	-0.10	-0.24 to 0.04	0.15
ESR	-0.10	-0.14 to -0.07	<0.001

JIA=juvenile idiopathic arthritis, ANA=anti-nuclear antibody, DMARDs=disease modifying anti-rheumatic drugs, PGA=physician global assessment, CHAQ=childhood health questionnaire, VAS=visual analogue scale, ESR=erythrocyte sedimentation rate

In etanercept-treated patients JADAS-10 decreased with a mean of -11.4 points (±7.2), and in adalimumab-treated patients JADAS-10 decreased with a mean of -8.3 points (±6.2). The predicted change in JADAS-10 in the adalimumab-treated patients did not differ significantly from the observed change in these patients (mean difference between the observed and predicted change in JADAS-10: -1.39 point(±4.9)).

Cox regression approach – hazard ratios for discontinuation

In unadjusted analyses the discontinuation rate for adalimumab-treated patients did not differ significantly from the discontinuation rate of etanercept-treated patients (HR 0.94 (95% CI: 0.43 to 2.03). Adjustment for the confounders (including year of inclusion) changed the HR to a certain extent, however there was still no significant difference between etanercept and adalimumab-treated patients (HR 1.96 (95% CI: 0.64 to 4.39). The unadjusted survival curves are shown in figure 1.

Fifty percent of etanercept users had discontinued treatment after 55 months, the follow-up of adalimumab treated patients was too short to reach the median survival.

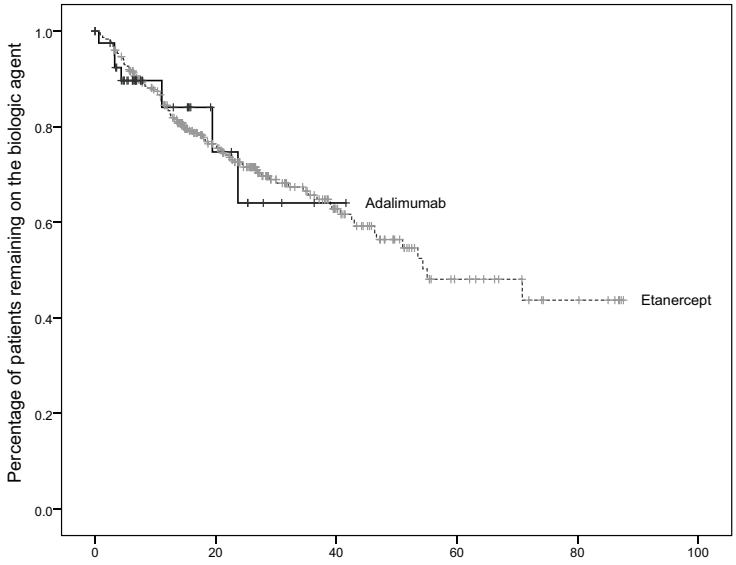

Figure 1 Unadjusted survival curve

Drug continuation of etanercept and adalimumab. Kaplan–Meier estimate of overall drug continuation until discontinuation due to ineffectiveness, adverse events or non-compliance. Vertical lines indicate censoring (censoring is defined as the time a patient discontinued treatment because of disease remission or, when still receiving the drug, the time of last study visit).

Propensity score approach – balancing confounders

Within a period of 4 months after starting treatment, 13% of etanercept treated patients achieved MDA vs. 29% of adalimumab treated patients. The initial balance of the prespecified confounders are shown in table 3. Significant imbalance existed in the variables PGA, number of active joints, number of limited joints, VAS patient, CHAQ score, ANA status, the number of patients with polyarticular course JIA and the number of patients with a history of uveitis. In table 3 both the standardized differences and the expected bias are given. The standardized difference is the difference between the groups on each variable in standard deviations. For example: the difference in means of CHAQ scores beteen the etanercept and adalimumab-treated groups is 0.4. Divided by the standard deviation of 0.7 this results in a standardized difference of 0.57. Although this gives us information on the differences between the groups, it does not inform us about the importance of this difference, i.e. the influence these differences would have on the achievement of MDA. The expected bias informs us about the amount of bias in the prediction of the achievement of MDA that we would expect if we would not balance the confounders. This is based on a regression on the outcome (MDA) in the etanercept-treated group. For example, we see in table that the adalimumab-treated group does not differ a lot from the etanercept-treated group in standard deviations, however the influence of this difference on the predicted outcome is relatively large.

Table 3 Initial balance of prespecified confounders

Variable	Mean in etanercept-treated (n=304)	Mean in adalimumab-treated (n=42)	Standardized differences	Expected bias (%)
Female gender	69%	67%	0.05	1.1
Age at onset of JIA	8	8.1	0.05	-0.2
Disease duration	3.9	4.2	0.08	-2.1
ANA positive	35%	52%	0.36	0.6
History of uveitis	4%	50%	1.20	74.3
Previous use of corticosteroids	36%	36%	0.003	-0.1
Number of previously used DMARDs	1	1	0.04	0.7
Polyarticular course JIA	74%	40%	0.72	-33.5
PGA	54	42	0.55	10.8
CHAQ	1.3	0.9	0.57	0.7
VAS patient	52	43	0.31	3.2
Number of active joints	10	6	0.47	8.3
Number of limited joints	7	4	0.31	17.7
ESR	21	17	0.21	-5.0

JIA=juvenile idiopathic arthritis; ANA=anti-nuclear antibodies; RF=rheumatoid factor; DMARDs=disease modifying anti-rheumatic drugs; MTX=methotrexate; PGA=global assessment of disease activity by the physician; CHAQ=childhood health assessment questionnaire; VAS=visual analogue scale; ESR=erythrocyte sedimentation rate; JADAS=juvenile arthritis disease activity score

The next step in the analysis using propensity scores was the actual construction of the propensity score, in which all the confounding factors are sufficiently balanced. Unfortunately, convergence was not reached in the construction of the propensity score model, which implied that there was too little overlap between the two groups to achieve an appropriate balance and construct a propensity score. Therefore the analysis was stopped here.

DISCUSSION

In the fast changing landscape of biologic treatment for JIA, data on comparative effectiveness are urgently needed. Using data from the Dutch ABC Register, this study attempted to compare the effectiveness of etanercept and adalimumab in the treatment of

(non-systemic) JIA. Three methods were applied. In a cox regression, the discontinuation rate of etanercept and adalimumab was comparable. A linear regression fitted in etanercept-treated patients and applied in the adalimumab-treated patients showed a similar decrease in JADAS-10, implying that the arthritis in the adalimumab treated patients would have responded in the same way, had they been treated with etanercept. These results seem to indicate that there is no difference in effectiveness between etanercept and adalimumab for JIA. However, in our opinion, the third analysis that was performed resulted in the most important findings. A less frequently used technique was applied – propensity score matching – for the evaluation of comparative effectiveness of the two biologic agents. One of the advantages of using this technique is that it informs us about areas of non-overlap in our data, which we do not recognize when we use the more popular techniques for controlling for confounding, such as the earlier mentioned regression methods. For the analysis we performed, the lack of overlap the method identified between the etanercept and adalimumab treated groups was a crucial problem. This minimal overlap between the two patient groups raises doubt as to whether it is possible to apply the other two methods. It may well be that the adalimumab-treated patients make up a separate patient group, who would not respond similarly to etanercept patients. Additionally, because adalimumab was a new drug, and therefore physicians were reluctant in prescribing it, the sample of adalimumab treated patients is much smaller than that of the etanercept treated patients. This limits the power for any of the analyses in detecting small differences in effectiveness. There is no doubt that the increasing treatment possibilities are good news for patients. Even for the previously most refractory patients, these treatment options mean that inactive disease may now be an achievable goal. Moreover, a more tailored treatment may be possible when we know which treatment is most effective and safe for which patient. Unfortunately, the increase in expensive treatments may also mean that health insurance providers will need to decide which treatment they will reimburse. To assure the freedom of prescription, to assure that the right patient gets the right drug and to inform clinical decision making when multiple drugs are available, reliable information on comparative effectiveness and safety is crucial. The results of the present study show how difficult it is to acquire such reliable information. This realization is very important for both researchers and prescribing physicians. The prescribing behavior of physicians has a large influence on the data from observational studies and the findings of observational studies also influence the choice of the prescribing physician. Especially in a rare disease such as JIA, the evidence is often limited to small case series and open label studies rather than large and well-designed comparative effectiveness studies. As said before, in JIA, very little research

has been performed investigating comparative efficacy/effectiveness of biologic agents. No direct head-to-head trials were conducted, and only a few investigators made attempts to compare trial results indirectly.[166 168 169] Head-to-head trials are not likely to be performed, the largest part of the evidence will have to come from observational studies. The two drugs in the present study have not been compared before in observational studies in JIA. This did happen in RA, in which it is easier to assess comparative effectiveness, not only because it is a more common disease, but also because RA is a much more homogeneous disease than JIA. Several studies assessed the comparative effectiveness of etanercept and adalimumab using observational data.[170-174] Various methods were used to correct for confounders. One study used propensity score methods and also found no differences in effect between the two TNF-inhibitors.[170] Others made use of different analyses and either found the two agents to be similarly effective [172] or adalimumab to be more effective than etanercept.[171 173 174] An explanation for these inconsistent results may be found in differences in the populations studied and the way outcomes were measured, but possibly also in the way confounders were controlled for.

The present study directs the attention to the importance of reliable comparative effectiveness studies, in which proper measures are taken to correct for confounding by indication. To reach a conclusion on the differences in effectiveness and safety large observational studies are needed. Extensive efforts should be made to identify the factors that influence the effectiveness of biologic agents and – just as important – also the prescribing practice of physicians treating JIA patients. A possibility of achieving the right balance between these possible confounders within an observational design would be to study these drugs in a population in which some randomness in the allocation of treatment consists, for instance in a country where different insurance companies reimburse only one of the two TNF-alpha inhibitors. It has to be kept in mind that whichever method would be used to control for confounding by indication, no method is able to control for unmeasured confounding.

Concluding, this is the first study attempting to assess the comparative effectiveness of two biologic agents in JIA patients. A lack of overlap between the two treatment groups interfered with the analyses performed, therefore no definite conclusions could be drawn. Confounding by indication is an important issue that needs to be accounted for in future analyses of the comparative effectiveness of two biologic agents in observational studies.

Chapter 4. **New developments in monitoring JIA**

Chapter 4.1 **The reliability of a patient-reported joint count in JIA**

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ABSTRACT

Objective. To evaluate the reliability of a mannequin-format patient-reported joint count in Juvenile Idiopathic Arthritis (JIA), and to detect changes in agreement at a second visit.

Methods. JIA patients aged 12-21 were asked to mark joints with active arthritis on a mannequin before their regular clinic visit. The physician then performed a joint count without having seen the patient's assessment. Agreement between scores of physician and patient-reported joint counts was assessed using Intraclass Correlation Coefficient (ICC). Kappa statistics were used to assess reliability of scoring individual joints.

Results. 75 JIA patients were included. In general patients had a low number of active joints (median 1 joint, indicated by the physician). ICC was moderate (0.61), kappas ranged from 0.3-0.8. At the second visit, kappas were similar; the ICC was 0.19. When a patient scored 0 joints, the physician confirmed this in 93-100%. When the patient marked ≥ 1 joints, the physician confirmed arthritis in 59-76%. Sensitivity to change was moderate.

Conclusion. Agreement between physician and patient on the number of joints with active arthritis was reasonable. Untrained patients tended to overestimate the presence of arthritis when they marked active joints on a mannequin-format joint count. When the patient indicated absence of arthritis, the physician usually confirmed this. As the agreement did not improve at follow-up, future research should focus on the possibility of achieving this through training. For now, the patient-reported joint count cannot replace the physicians' joint count in clinical practice; it may be used in epidemiological studies with caution.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is one of the most common chronic auto-immune diseases in childhood, affecting 47-87 per 100.000 children, which requires regular monitoring.[80 175] One method of monitoring is gathering information from patients themselves, through a patient-reported outcome (PRO) measure. PROs can be a useful tool to observe disease activity between clinic visits, increase patient involvement and also aid in epidemiological surveys. Therefore they are increasingly being developed and applied.[176-178]

One of these PROs is the self-reported joint count, the use of which has extensively been investigated in studies in patients with RA. Conclusions on agreement between patient-reported and physician-reported joint counts are mixed. Results vary between good and poor to moderate agreement. A mannequin format, in which patients indicate which joints are inflamed on a figure, generally yields higher scores than a text format.[179]

Only two studies have been performed investigating self-reported joint counts in JIA, one using a text format and one using a mannequin format.[180 181] On the text-format joint count agreement between physicians and patients/parents on individual joints was moderate, the investigators therefore concluded that this joint count could not replace the physician's assessment.[181] The mannequin format was used in a study investigating whether patients could discriminate active from inactive disease; patients seldom missed arthritis but frequently overestimated disease activity. The overall agreement and the agreement on individual joints were not described. Both these studies were of cross-sectional nature, only describing the first time patients were confronted with a joint count.

The aim of the current study was to evaluate the agreement between physician and self-reported active joint counts by JIA patients using a mannequin and to determine whether the agreement between the physician and the patient changed over time.

METHODS

Data were collected prospectively at the JIA-outpatients clinic at the Erasmus MC, a tertiary referral center in Rotterdam, The Netherlands. All consecutive JIA patients aged 12-21 fulfilling the ILAR criteria who visited the clinic between February 2013 to February 2014 were invited to participate.[1] The study was performed according to regulations of the local ethical committee. At a regular clinic visit, patients were first asked to mark the joints they felt to have active arthritis on a figure. Active arthritis was defined as swelling within a

Name: ……

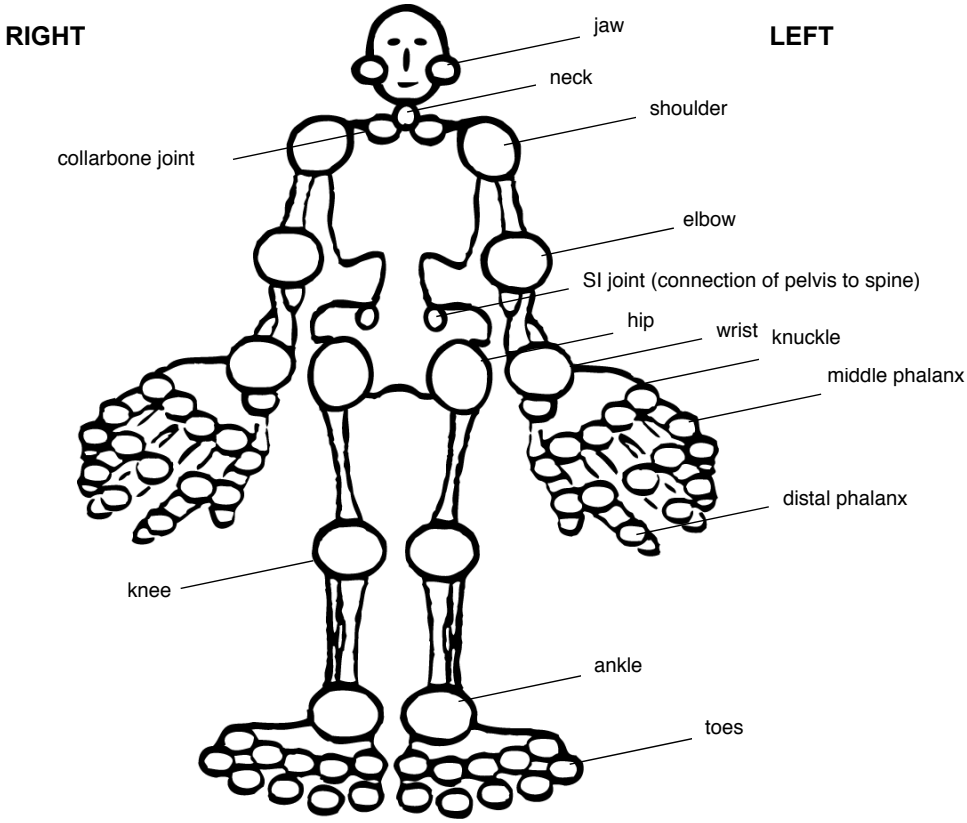
Date: ……..……

Mannequin joint count: which joints are currently inflamed?

Please mark the joints where the arthritis is currently active (where there is inflammation) on the mannequin below.
A joint is considered to be inflamed when at least two of the following criteria are present:

- pain
- swelling
- limited motion.

Note: if a joint is always restricted, but none of the other two features are present, you don't need to mark it.



☐ I have no complaints, none of my joints are inflamed.

Figure 1 Mannequin joint count form as filled out by the patients (translated from Dutch)

joint, or limited range of motion accompanied by joint pain or tenderness.[1] The definition of active arthritis was provided on the figure (figure 1).
No additional information was given. After the patient had filled out the mannequin, the pediatric rheumatologist (PhvP) performed a formal joint count, without having seen the patient's assessment. This practice continued during follow-up, giving patients an indirect feedback moment during each following visit and minimum education to see how the agreement would change naturally over time. The following joints were taken into account: temporomandibular, cervical spine, shoulder, sternoclavicular, elbow, wrist, MCP's, PIP's and DIP's (analyzed both separately and as a unit(hand)), back, SI joints, hip, knee, ankle, MTP's and phalanges of the foot (analyzed both separately and as a unit (foot)). The acromioclavicular and subtalar joints were not evaluated, because they were judged to be too difficult to assess.
Additionally, patients were asked to fill out a Child Health Assessment Questionnaire (CHAQ),[182] including Visual Analogue Scales (VAS, ranging from 0-100) for wellbeing and pain. Demographic data and data on disease history were collected from the charts.

Statistical analysis

For both the first as the second visit, agreement was assessed in various ways. For level of agreement on the number of active joints a two-way random single measure absolute agreement ICC was used. We used the following interpretation for Cohen's kappa and ICC: <0.40=poor, ≥0.40–0.60=moderate, >0.60-0.80=substantial and >0.80=good reliability.[183] Kappa statistics were used for calculating agreement on individual joints. Additionally, the overall agreement and the positive/negative agreement proportion per joint were computed.[184] Overall agreement is the percentage of joints that were scored identically by physician and patient. The positive agreement is the number of joints that were scored as being active by both physician and patient, divided by the average number of joints scored positive. The negative agreement is the number of joints scored as inactive by both parties, divided by the average number of joints scored negative. Negative agreement was expected to be high, as most joints were expected to be scored inactive.
We calculated that a sample size of 59 subjects with 2 observations per subject achieves 80% power to detect an ICC of 0.6 (ρ_1) when the ICC was assumed to be at least more than 0.35 (ρ_0) using an F-test with a significance level of 0.05.[185]
To evaluate whether patients could discriminate between inactive and active arthritis, taking the physician joint count as reference, the (positive and negative) predictive values of a patient scoring 0 active joints or >0 active joints were calculated. In addition, sensitivity and

specificity were calculated, enabling us to compare our results to previous research done on this subject.

For the assessment of construct validity, Spearman's rho correlation coefficient was calculated to test the correlation between VAS scores and the number of affected joints indicated on the two joint counts. To test the difference between the various correlation coefficients over time the Fisher r-to-z transformation was used. Correlation coefficients were interpreted as follows: ≤0.3=weak, 0.4-0.6=moderate, ≥0.7=strong.

Absolute and proportional changes in total joint count scores between the first and the second visit were calculated for both the patient-reported and physician-reported joint counts. Consequently, sensitivity to change was assessed using two kinds of coefficients.[186] Firstly, Pearson's correlation coefficient was used to assess the correlation between absolute changes in patient and physician-reported joint counts, for the total group of patients. In addition the ICC of the change scores was calculated. Secondly, patients were divided in three groups (improved, stable and worsened), according to the change in the physician-reported joint counts. Standardized response means (SRM) were calculated for the groups that improved or worsened, based on the mean proportional change in the patient-reported joint counts, and its standard deviation.

Descriptive statistics were reported as absolute number, median with IQR or mean with range as appropriate. Data were analyzed using the IBM SPSS statistics for windows package, version 21.0 (Armonk, NY: IBM Corp.).

RESULTS

Patient characteristics

Of 80 patients who agreed to participate, only 75 could be used for the analysis of agreement, because in 5 patients the physician did not perform a full formal joint count. Characteristics of all 75 consecutive patients are shown in table 1.

Table 1 Patient and disease characteristics at the first visit (n=75)

Characteristics	
Age (in years), median (IQR)	16.0 (14.7-17.8)
Disease duration (in years), median (IQR)	3.7 (0.9-8.7)
Female, n (%)	54 (72)
JIA category, n (%)	
Systemic	5 (7)
Oligoarticular persistent	17 (23)
Oligoarticular extended	7 (9)
Polyarticular RF+	12 (16)
Polyarticular RF-	18 (24)
Psoriatic arthritis	9 (12)
Enthesitis-related arthritis	6 (8)
Undifferentiated arthritis	1 (1)
Laboratory blood tests, n (%)	
ANA+	27 (36)
HLA-B27+	13 (17)
RF+	12 (16)
CCP+	11 (15)
History of uveitis, n (%)	11 (15)
Disease activity Variables, median (IQR)	
ESR date visit	9 (3-23)
CHAQ date visit	0.375 (0.000-0.875)
VAS physician	8 (0-28)

IQR=interquartile range; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; ESR=erythrocyte sedimentation rate; CHAQ=Childhood Health Assessment Questionnaire; VAS=visual analogue scale.

None of the patients refused to participate. Of 53 patients a second measurement was present. The inferences on the second visit are discussed in a separate paragraph below. Patients with a second visit did not differ from patients without a second visit with regard to disease activity at the first visit. Patients had a median age of 16 years (IQR 15-18) and an average disease duration of 3.7 years (IQR 0.9-8.7). Overall disease activity was low, both physician and patients indicated low disease activity on a VAS (median <20). The distribution of JIA categories was representative for an outpatient clinic patient population within these age ranges.

Agreement at the first measurement

The median number of active joints scored by the physician was 1 joint (IQR 0-3). The patients scored a median of 2 joints (IQR 1-5). The ICC was moderate with a value of 0.61 (95% CI: 0.43-74). Adolescents (aged 12-17 years, n=44, ICC: 0.69 (95% CI: 0.48-0.83)) appeared to agree more with their physician than young adults (aged 18-21 years, n=31, ICC: 0.45 (95% CI: -0.14-0.69), although not statistically significant. Comparable estimates were found for patients with short disease duration (≤1 year, n=19) and patients with longer disease duration (n=56) with respective ICC's of 0.69 (95% CI: 0.35-0.87, n=19) and 0.45 (95% CI: 0.21-0.63, n=56). Agreement between patients and physicians on individual joints is reported in table 2, kappa values ranged from 0.3-0.7.

Table 2 Agreement on individual joints at the first visit (n=75)

Joint	Kappa value	Overall agreement in %	Positive agreement in %	Negative agreement in %	Total no. of times joint is scored positive by physician (n=75) (%)	Total no. of times joint is scored positive by patients (n=75) (%)
Shoulder left	0.38	89	43	94	4(5)	10(13)
Shoulder right	0.28	89	33	94	5(7)	7(9)
Elbow left	0.58	93	62	96	7(9)	6(8)
Elbow right	0.64	95	67	97	5(7)	7(9)
Wrist left	0.68	89	75	93	15(20)	17(23)
Wrist right	0.65	88	73	92	17(23)	016(21)
Hand left	0.44	85	48	91	9(12)	14(19)
Hand right	0.39	81	44	92	12(16)	16(21)
Hip left	0.57	95	60	97	4(5)	6(8)
Hip right	0.57	95	60	97	4(5)	6(8)
Knee left	0.51	79	65	85	18(24)	28(37)
Knee right	0.41	75	56	82	15(20)	28(37)
Ankle left	0.47	87	55	92	9(12)	13(17)
Ankle right	0.34	88	40	93	5(7)	10(13)
Foot left	0.31	95	36	99	5(7)	6(8)
Foot right	0.47	95	50	97	4(5)	4(5)

Individual hand and foot joints, temporomandibular joints, cervical spine, sternoclavicular joints and the SI joints were omitted due to distorted or negative kappa values.

Overall agreement was generally around 90% or higher. The agreement for the knees was lower; 75% for the right knee and 79% for the left knee. Differences in agreement between the left and right hand side occurred in other joints too. Positive agreement was generally poor to reasonable (33-75%, lowest scores for the shoulders) whereas negative agreement was excellent (82-99%, lowest scores for the knees). This last finding was expected, as disease activity was low and therefore most joints would be negatively scored.
In table 3 scores are compared between patients' and physicians' results of the first time they scored the mannequin, depending on the number of active joints scored: 0, 1, 2-4, 5-10, or more than 10 joints.

Table 3 Agreement on number of joints between physician and patient at the first visit

Physician JC / Patient JC	0 joints	1	2-4	5-10	More than 10	Total JC patient
0 joints	18	0	0	0	0	18
1	7	7	4	0	0	18
2-4	7	5	6	1	1	20
5-10	0	2	2	3	1	8
More than 10	0	0	3	4	4	11
Total JC physician	32	14	15	8	6	75

Agreement is indicated by the shaded areas. JC=joint count

In all five groups patients mostly overestimated the number of active joints. Underestimation of the total number was less common. When over or underestimation occurred, this remained confined to the closest categories of number of joints.
The presence of arthritis was indicated by 14 of 31 patients where the physician found no arthritis. The knees were the most marked joints in this group (n=11). The VAS pain of these patients was higher than VAS pain of patients who agreed with the physician on inactive disease (median VAS pain 18 vs 0, p=0.005, Mann-Whitney-U). Possible explanations for the overestimation were: residual complaints after recent arthritis/structural damage in 5 patients, pain after high physical activity in 4 patients, enthesitis/tendinitis in 2 patients. Three patients had arthritis within two months after this visit, and one patient did have arthritis on ultrasound evaluation. In these three patients, the physician may have missed arthritis on examination.
Taking the physician's joint count as a reference, the predictive value of a patient scoring

0 active joints was 100%. This means that when a patient scored inactive disease, the physician generally indicated there was no arthritis (negative predictive value). When a patient did score a number of active joints, only in 76% the physician agreed there was arthritis present (positive predictive value). Sensitivity and specificity were 100% and 56%, respectively. Sensitivity, specificity and negative and positive predictive value for discriminating inactive from active disease did not change when only the most affected joints (shoulders, elbows, wrists, hands, hips, knees, ankles and feet) were used.

Construct validity

We performed Spearman correlations to test the correlations between the several VAS' and the joint counts. The physician-reported joint count correlated very well with the patient-reported joint count and the VAS physician (both a Spearman's rho of 0.80 and 0.79 respectively), but less well with the VAS wellbeing of the patient (Spearman's rho of 0.61 and 0.65). The patient-reported joint count correlated moderately with the VAS wellbeing (Spearman's rho of 0.49) and with the VAS pain (Spearman's rho of 0.64).

Longitudinal agreement and sensitivity to change

At the second visit, the median number of active joints reported was 0 (IQR 0-3) joints for physicians and 2 (IQR 0-6) joints for patients. The ICC that was estimated was 0.192 (95% CI: -0.051 to 0.424). The confidence interval indicated a possible negative value of the ICC, which was caused by a large variation in between and within subject variability. The interpretation of this ICC can only be that there is very low agreement.[187] We suspected this was caused by 4 subjects a with a very large discordance between physician and mannequin joint count. These patients all scored 30 or more active joints, while the physician scored 0-10 joints. The ICC with these subjects removed was still low; 0.30 (95% CI: 0.04-0.53). Kappa values were similar during follow-up compared to the first time of marking active joints on the mannequin. Negative predictive value for the second visit was 93%, positive predictive value was 59%. Sensitivity was 96% and specificity 45%.
At the second visit, the physician indicated inactive disease in 29 patients, 16 of which did not agree. This is a slightly higher percentage than at the first visit. The negative predictive value was slightly lower than at the first visit, because1 patient indicated inactive disease where the physician did find arthritis on physical examination. This patient indicated to have no complaints. The physician joint count did indicate improvement from the previous visit, however the disease was not fully inactive.
At the second visit we found the patient-reported joint count to have a stronger correlation

(p<0.05) with VAS wellbeing (0.75) and to have a weaker correlation with physician joint count (0.36) compared with the first visit (0.49 and 0.8 respectively). Other correlations did not change significantly during follow-up.
The absolute changes in physician and patient-reported joint counts were moderately correlated (Pearson's rho: 0.436, p=0.001). The ICC for the change-scores was 0.305 (95% CI: 0.051-0.526). The SRM for the proportional change in patient-reported joint counts was moderate (0.67) in patients who worsened according to the physician. The SRM for patients who improved according to their physician was low (0.23). Therefore the patient-reported joint count appeared to be most sensitive to change for patients whose disease became more active over time.

DISCUSSION

This study is one of the first to investigate whether a patient-reported joint count based on a mannequin format can be used as a PRO in JIA. The overall agreement between the physician and the patient total joint count was found to be moderate (ICC 0.61) the first time patients filled out the mannequin. Agreement on individual joints was moderate to good, depending on the joint (kappa 0.3-0.7). At the second visit the kappa values stayed stable, however the ICC decreased during follow-up. Construct validity was high, however the second time patients filled in the joint count, the correlation to general wellbeing scores and pain was higher and the correlation to the physician joint count was lower than the first time. Patients tended to overestimate the presence of arthritis. A patient-reported joint count indicating full absence of arthritis nevertheless proved to be highly reliable. These results were consistent over time. Sensitivity to change over time proved moderate, and was highest in patients whose disease worsened.
Two other studies have investigated patient-reported joint counts in JIA patients. The first one tested a text-format joint count in a very large group of patients and parents of patients with JIA.[181] In a conference abstract, it reported agreement on individual joints ranging from 0.15 for the shoulder to 0.69 for the cervical spine. In general, these kappa values are comparable to the ones found in the present study. The most frequently scored joints often had the highest kappa values.
The second study investigating patient-reported joint counts in JIA used the same mannequin format as the present study.[180] The study used this format, however it focused on the question whether patients could distinguish between active and inactive disease, and did not evaluate agreement on individual joints or total joint scores. Additionally it did

not focus solely on patients, but investigated patient and parent assessment. Sensitivity was comparable and specificity slightly lower than the specificity we found. With regard to the ability of patients to discriminate between inactive and active disease, the authors reach the same conclusion: patients did not miss arthritis, however overestimated the presence of it frequently.

Overall agreement has not been investigated in studies with JIA patients. In adult RA patients this has been done and the ICCs of RA patients with their physicians were comparable to the ICC found in the present study.[179] It has to be kept in mind however that ICCs do not generalize well from one study to another, because they are strongly influenced by the variance in the population it is measured in.

RA and JIA patients have been shown to overestimate their disease activity compared to the physician's estimation also on other disease activity scales.[188 189] The reason for this overestimation is not clear but it has been suggested that high functional disability and pain might influence this discordance.[179 189] Also in this study, patients who agreed with their physician on the inactivity of the disease had lower pain scores than patients who indicated disease activity where the physician did not. There was no significant difference in CHAQ scores between the two groups. Patients may have difficulty distinguishing pain caused by active arthritis from pain as a result of other causes. Although radiological joint damage is relatively uncommon in the pediatric population, structural damage could be a cause of pain, as could muscular strain.[36 190] Persistent pain and the subsequent sensitization of the central nervous system have been proposed to cause a lowering of the pain threshold and altered pain perception in JIA patients.[191 192] This could be an alternative explanation for reported pain uncorrelated to disease activity indicated by the physician. It could also partly explain the high correlation between the patient-reported joint count and the VAS pain. Before considering implementation of a patient-reported joint count, the reasons for overestimation should be more thoroughly investigated. The purpose of the use of a patient-reported joint count in clinical practice also has to be clearly defined. Armbrust et al. used the joint count as a general assessment of disease activity, which only makes the distinction between active and inactive disease. In that respect, we found that the patient-reported joint count predicts the activity as marked on the physician joint count better than the VAS for general wellbeing does. If the patient-reported joint count would be used for this purpose, one could consider only using the most affected joints, as the discriminative performance did not change when only these joints were taken into account. For this purpose it is encouraging, that even without training, patients can generally be trusted when they indicate inactive disease.

The other option is to use the joint count not only to discriminate between active and inactive disease, but to actually monitor disease activity over time. The possibility to monitor their disease activity, may stimulate patients' self-management and their adherence to therapy.[193] For this purpose, it is reassuring that the sensitivity to change was highest in the group that worsened. In addition, although the agreement on overall and individual joints was only moderate, we have to keep in mind that two physicians examining the same patient agree to the same extent (moderately) on the presence of active or inactive disease.[194 195] Still, ideally we would like to improve the absolute agreement between physician and patient, so that all changes in disease activity can be monitored accurately. This could be done by means of a training program. Training RA patients to examine their own joints had a positive effect on the reliability of patient-reported joint counts.[196]

The way the mannequin should be filled out is also a question to be answered. The addition of a "doubt" option, did not seem to add to the discriminative power of the mannequin, but this may change with training.[180] Also one could question whether the patient would have to mark every joint as the patients did in the study by Armbrust et al., as the results with regard to predictive value and sensitivity and specificity did not differ much from those we found in the current study. Only marking the active joints seems to be sufficient, and is less time consuming.

For the use in epidemiological surveys the agreement found seems to be acceptable, although one should realize that the obtained estimate of disease activity is not flawless. In this setting a more general indication of disease activity is sufficient, as the main objective is to describe disease status on a population level and no individual decisions are based on these data.

For generalization of the results from the present study it has to be taken into account, that the JIA population in this study was 12 years and older and sampled at a tertiary referral clinic. Furthermore, consecutive (and therefore mostly already treated) patients visiting our clinic were included, resulting in a fairly homogeneous population with regard to disease activity, which was generally low.

When interpreting the results from this study, it has to be kept in mind that the examination by the physician is not flawless either.[194 195] Although imaging techniques are increasingly being applied in pediatric rheumatology, for most modalities no reference standards are available yet. So, even though it seems that ultrasound and other techniques could be of help in identifying subclinical arthritis, the scoring systems used still need more validation before they can be used extensively to guide clinical practice.[197] In future studies, in addition to including a training program, also multiple physicians could assess the patients,

so that a more reliable physician joint count could be obtained.
Because they received no training, patients may have made mistakes while filling out the joint count. Despite the mannequin clearly stating which side was left and which was right, some patients might have filled in the form the wrong way round, thereby causing an overall lower positive agreement. In addition, patients may not have been aware of the existence of referred pain, and may have indicated the wrong joint to be active (for instance in the case of the hip-knee).
The ICC of the second measurement was much lower than the ICC of the first measurement. We provided an estimate for the ICC without four outliers, because the ICC that was estimated for the whole group was unreliable. For an unknown reason at the second measurement there were more outlying values, causing the within-subject variability to be disproportionate to the between-subject variability. The correlation between the physician joint count and the patient-reported joint count also changed. The patient-reported joint count correlated more with the VAS pain. Apparently these patients were more likely to fill out the mannequin, marking the joints with pain instead of those with active arthritis.
In conclusion, agreement between physician and patient-reported joint counts was moderate. Especially a joint count of zero by the patient was predictive of the joint count of the physician. This PRO can therefore not fully replace the physician's joint count at a regular clinical visit.
The mannequin joint count could be used to aid in epidemiological surveys, as it gives a reasonable estimate of the true number of active joints. Before being implemented in a clinical setting, more research is needed to determine whether agreement can be improved by training and whether the patient-reported joint count is then also better able to detect changes over time.

Chapter 4.2 **Automated determination of bone age and bone mineral density in JIA patients: a feasibility study**

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ABSTRACT

Introduction. Chronic inflammation combined with glucocorticoid treatment and immobilization puts juvenile idiopathic arthritis (JIA) patients at risk of impaired growth and reduced bone mineral density (BMD). Conventional methods for evaluating bone age and BMD are time-consuming or come with additional costs and radiation exposure. In addition, an automated measurement of bone age and BMD is likely to be more consistent than visual evaluation. In this study, we aimed to evaluate the feasibility of an automated method for determination of bone age and (cortical) bone mineral density (cBMD) in severely affected JIA patients. A secondary objective was to describe bone age and cBMD in this specific JIA population eligible for biologic treatment.

Methods. In total, 69 patients with standard hand radiographs at the start of etanercept treatment and of calendar age within the reliability ranges (2.5 to 17 years for boys and 2 to 15 years for girls) were extracted from the Dutch Arthritis and Biologicals in Children register. Radiographs were analyzed using the BoneXpert method, thus automatically determining bone age and cBMD expressed as bone health index (BHI). Agreement between measurements of the left- and right-hand radiographs and a repeated measurement of the left hand were assessed with the intraclass correlation coefficient (ICC). Regression analysis was used to identify variables associated with Z-scores of bone age and BHI.

Results. The BoneXpert method was reliable in the evaluation of radiographs of 67 patients (radiographs of 2 patients were rejected because of poor image quality). Agreement between left- and right-hand radiographs (ICC = 0.838 to 0.996) and repeated measurements (ICC = 0.999 to 1.000) was good. Mean Z-scores of bone age (–0.36, $P = 0.051$) and BHI (–0.85, $P < 0.001$) were lower compared to the healthy population. Glucocorticoid use was associated with delayed bone age (0.79 standard deviation (SD), $P = 0.028$), and male gender was associated with a lower Z-score of BHI (0.65 SD, $P = 0.021$).

Conclusions. BoneXpert is an easy-to-use method for assessing bone age and cBMD in patients with JIA, provided that radiographs are of reasonable quality and patients' bone age lies within the age ranges of the program. The population investigated had delayed bone maturation and lower cBMD than healthy children.

INTRODUCTION

Chronic inflammatory diseases such as juvenile idiopathic arthritis (JIA) can influence bone development. Continuous exposure to inflammatory cytokines, together with glucocorticoid therapy, affects bone formation. This combined with decreased physical activity and pubertal delay puts JIA patients at risk of impaired growth and reduced bone mineral density (BMD).[198 199] The pediatric rheumatologist needs to be aware of both the bone age and the BMD of JIA patients in order to take this into account in choosing the best therapy. The assessment of bone age is usually made using the Greulich and Pyle atlas.[200] Dual-energy X-ray densitometry (DXA) is the most commonly used method of assessing BMD.[201] Recently, BoneXpert was developed, bringing back the use of radiogrammetry, one of the oldest methods for assessing BMD.[202] This new digital X-ray radiogrammetry (DXR) method combines the assessment of bone age with a radiogrammetric measurement of (cortical) BMD (cBMD) of the second to fourth metacarpal joints. The cBMD is expressed by BoneXpert as a Bone Health Index (BHI), in which cBMD is corrected for size. The BoneXpert method makes use of conventional radiographs of the hand, thereby making it attractive for pediatric use because of its simple application, relatively low costs[203] and lower effective radiation dose compared with other methods. Normative data are available because the method was validated in a healthy pediatric population.[204 205] The application has not been tested in JIA patients, in whom long-standing inflammation of the wrist can lead to growth abnormalities and destruction of the bone, thereby possibly complicating the assessment of bone age and bone health. Utilization of the Dutch Arthritis and Biologicals in Children (ABC) register provides a unique way to evaluate this method in a severely affected JIA population eligible for biologic treatment. Our objective in this study was to evaluate the feasibility of an automated method for the determination of bone age and cBMD in severely affected JIA patients. A secondary objective was to describe bone age and cBMD in this specific JIA population eligible for biologic therapy.

METHODS

Patient selection

Patients from two centers participating in the Dutch ABC register who were prospectively enrolled between 1999 and 2012 were eligible for this study. Biologic-naïve patients were selected, starting etanercept, of whom a standard radiograph of both hands and wrist in the posteroanterior view was made at the start of treatment (that is, 1 year before to 3 months

after starting etanercept). The participants' calendar age had to be within the reliability range of the BoneXpert method (that is, 2.5 to 17 years for boys and 2 to 15 years for girls). Ultimately, the radiographs of 69 patients were eligible for automatic analysis by BoneXpert. A flowchart of the patient selection is provided in Additional file 1.

Clinical data collection

The ABC register, a multicenter, prospective, observational study, aimed to include all children diagnosed with JIA in whom biologic treatment was being initiated. Informed consent was obtained from all patients older than 12 years of age, in addition to the parents or guardians of all patients younger than 16 years of age. The study protocol was centrally approved by the Medical Ethics Committee of the Erasmus MC, and local permission was obtained from the ethical bodies in the two other participating hospitals (Academic Medical Center and Reade). From the ABC register, patient and disease characteristics were collected at baseline, including data on disease activity from the following sources: physician's global assessment of disease activity on a visual analogue scale (VAS) (range from 0 to 10 cm, with 0 being the best score); Childhood Health Assessment Questionnaire (CHAQ) (range from 0 to 3, with 0 being the best score) by patients and/or their parents, including global assessment of well-being and pain on a VAS (range from 0 to 10 cm, with 0 being the best score); number of joints with active arthritis and joints with limited motion; and erythrocyte sedimentation rate (ESR). Using these variables, the Juvenile Arthritis Disease Activity Score in 10 active joints (JADAS-10) was calculated. The scale from 0 to 40 represents the simple linear sum of the scores of the physician and parent and/or patient global assessment, an active joint count (up to 10 joints) and a normalized value of ESR to a 0 to 10 scale.[23]

Image analysis

The stand-alone Windows product of BoneXpert (BoneXpert Version 2.1.0.12; Visiana, Holte, Denmark) was used to analyze the hand radiographs. BoneXpert automatically generates the following outcome variables: (calendar) age, bone age based on Greulich and Pyle, Z-scores of bone age (compared with a healthy reference population),[206] BHI and Z-scores of BHI.[202] BHI is based on the cortical thickness (T) of the three middle metacarpals. In the construction of BHI, metacarpal width (W) and length (L) are also incorporated to compensate for the high variation in stature of growing children, as expressed in the following formula:[202]

$$BHI = \pi T (1 - T/W) / (LW)^{0.33}$$

The radiographs included the complete hand and wrist joints of both the left and right sides. All images were collected as a DICOM files from three different centers. If the radiographs were available only on conventional films, they were digitized with a Sierra Plus scanner (VIDAR Systems, Herndon, VA, USA) and converted to a 300-dpi DICOM file. During the analytical process in BoneXpert, possible error messages were noted. The left-hand radiograph was uploaded and analyzed in BoneXpert a second time in order to be able to determine its test–retest reliability.

Statistical analysis

Descriptive statistics are reported in terms of absolute numbers, median and interquartile range (IQR) or mean and standard deviation (SD). The single measure intraclass correlation coefficient (ICC) and Bland-Altman plots were used to determine the agreement of the outcome variables of the BoneXpert method.

To determine whether the Z-score of bone age and the Z-score of BHI were different from those in the healthy population, a one sample *t*-test was used. Univariate linear regression analysis was performed to identify variables associated with the Z-score of bone age and the Z-score of BHI. Because of the small sample size, only a limited number of variables could be tested. The prespecified variables entered into the univariate model were age, sex, JADAS-10, disease duration and use of systemic glucocorticoids, defined as “ever use” or “never use”. All analyses were performed with SPSS version 20 software (SPSS, Chicago, IL, USA).

RESULTS

Feasibility

A standard hand radiograph of both hands was available for 69 patients starting etanercept treatment. The calculations of bone age and BMD by BoneXpert took a few seconds. BoneXpert rejected the radiographs of two patients because of poor image quality, resulting in available BoneXpert outcomes of 67 patients. In three patients, an error message indicating uncertainty of bone age was given by BoneXpert; these patients had calendar ages within the BoneXpert age ranges (2.5 to 17 years for boys and 2 to 15 years for girls), but their bone age came out of the analysis to be outside these age ranges, resulting in an error message. However, BoneXpert produced all outcome variables in these three patients, except for a missing Z-score of BHI in one patient.

The ICC of the agreement of all outcome variables between the left and right hand

radiographs varied from 0.838 to 0.996. Bland-Altman plots of the agreement between left and right hand radiographs are provided in Additional file 2. The ICC of the agreement of repeated measurements of all left-hand radiographs on Z-scores of bone age and BHI varied from 0.999 to 1.000.

Patient and disease characteristics

Patient and disease characteristics of the 67 patients who could be evaluated with BoneXpert are presented in Table 1. Disease activity of these patients was moderate to severe at the time the hand radiographs were made (mean JADAS-10 score = 21 ± 5).

Table 1 Patient and disease characteristics at start etanercept

Baseline characteristics	n=67
Female, n (%)	36 (54)
Age at onset JIA in years, mean (±SD)	8.5 (± 3.8)
Age at start etanercept, mean (±SD)	11.0 (± 3.1)
JIA disease duration before start etanercept in years, median (IQR)	1.8 (1.1-3.8)
ANA positive, n (%)	14 (21)
Category JIA, n (%)	
Systemic JIA	4 (6)
Polyarticular RF negative	27 (40)
Polyarticular RF positive	9 (13)
Oligoarticular extended	18 (27)
Psoriatic arthritis	5 (8)
Enthesitis related arthritis	4 (6)
Previously used medications, n (%)	
Systemic prednisone	32 (48)
Methotrexate	66 (99)
DMARD other than MTX	14 (21)
Concomitant co-medication at start biological, n (%)	
Systemic prednisone	26 (39)
Methotrexate	64 (96)
DMARD other than MTX	2 (3)
Disease activity parameters at baseline, median (IQR)	
VAS physician (0-10 cm; 0 best score)	6.5 (5.0-7.4)
CHAQ total (0-3; 0 best score)	1.50 (0.90-2.10)
VAS pain (0-10 cm; 0 best score)	6.3 (2.4-7.7)
VAS wellbeing (0-10 cm; 0 best score)	6.1 (3.2-7.4)
Active joints	11 (7-18)
Limited joints	6 (3-13)
ESR	11 (5-29)
JADAS-10 (0-40), mean (±SD)	21 (± 5)
Ever hand or wrist involvement, n (%)	64 (96)
Z-score of BA, mean (±SD)	-0.36 (± 1.44)
Z-score of BHI, mean (±SD)	-0.85 (± 1.15)*

* significantly different from 0 at the $p < 0.05$ level.

JIA=juvenile idiopathic arthritis; ANA=anti-nuclear antibodies; RF=Rheumatoid Factor; MTX=methotrexate;

DMARD=disease modifying anti-rheumatic drug; VAS=visual analogue scale; CHAQ=child health assessment questionnaire; ESR=erythrocyte sedimentation rate; JADAS=juvenile arthritis disease activity score; BA=Bone Age; BHI=Bone Health Index; Z-score=standard deviation score compared with healthy population.

Bone maturation was delayed compared with the normal population, but not significantly (mean Z-score of bone age = –0.36 (±1.44), $P = 0.051$). Bone maturation was greatly impaired (below –2 standard deviations (SD)) in eight patients, and three patients had highly accelerated bone maturation (above +2 SD). The mean Z-score of bone age was strongly influenced by one patient with a very high bone age (+5 SD), who had long-standing severe polyarticular enthesitis-related arthritis. When this patient was left out of the analysis, the mean bone maturation of the remaining patients was significantly delayed (mean Z-score of bone age = –0.45 (±1.28), $P = 0.008$). Compared with the normal population, the cBMD was lower (mean Z-score of BHI = –0.85 (±1.15), $P < 0.001$). Ten patients had a Z-score of BHI less than –2 SD.

Regression analysis

A univariate linear regression analysis of bone age and BHI was performed to investigate which variables were associated with the Z-score of bone age and the Z-score of BHI (Tables 2 and 3). Glucocorticoid use was associated with a lower Z-score of bone age (0.79 SD, $P = 0.028$). Only male gender was significantly associated with the Z-score of BHI; being a boy lowered the Z-score of BHI of 0.65 points ($P = 0.021$).

Table 2 Univariate regression coefficients of baseline variables with the Z-score of bone age

Baseline variable	Estimated beta	95% CI	p-value
Age	0.024	-0.116 – 0.164	0.736
Male gender	-0.190	-0.921 – 0.541	0.605
Disease duration	-0-030	-0.184 – 0.1234	0.694
CHAQ	-0.021	-0.577 – 0.534	0.940
JADAS-10	0.008	-0.065 – 0.081	0.830
Ever use of systemic glucocorticoids	-0.790	-1.492 – -0.088	0.028

CHAQ=child health assessment questionnaire; JADAS=juvenile arthritis disease activity score; BHI=Bone Health Index; Z-score=standard deviation score compared with healthy population.

Table 3 Univariate regression coefficients of baseline variables with the Z-score of BHI

Baseline variable	Estimated beta	95% CI	p-value
Age	0.067	-0.024 – 0.159	0.147
Male gender	-0.649	-1.197 – -0.102	0.021
Disease duration	0.040	-0.080 – 0.160	0.505
CHAQ	0.008	-0.420 – 0.436	0.971
JADAS-10	-0.036	-0.094 – 0.023	0.224
Ever use of systemic glucocorticoids	-0.340	-0.904 – 0.224	0.233

CHAQ=child health assessment questionnaire; JADAS=juvenile arthritis disease activity score; BHI=Bone Health Index; Z-score=standard deviation score compared with healthy population.

DISCUSSION

Application of the BoneXpert automated method for assessing bone age and cBMD in JIA patients proved to be feasible. Its use was easy and fast, and the program rejected few radiographs. The Z-scores of bone age and BHI were found to be impaired in the population of JIA patients evaluated in this study compared with a healthy population. In addition to its validation in a healthy pediatric population,[204 205] bone age measurement using BoneXpert has been evaluated in pediatric patients of short stature, children with precocious puberty and patients with congenital adrenal hyperplasia.[207-209] In these patient groups, in whom bone maturation is likely to be affected, the BoneXpert bone measurement method proved feasible. We had anticipated a higher number of rejections by the BoneXpert program relating to growth abnormalities, periarticular abnormalities and deviation of bone age commonly found in severely affected JIA patients.[190 210-212] Unexpectedly, BoneXpert rejected no radiographs because of these abnormalities. Besides the two rejections due to poor image quality, only one radiograph with extremely accelerated bone maturation resulted in absence of a Z-score of BHI. The low rejection rate is advantageous; however, one has to take into account that patients outside the age ranges of the program had to be excluded, who were composed mostly of older patients (older than 15 years of age for girls and older than age 17 years for boys). For follow-up of patients, it would be useful if a BHI reference existed for children who have reached skeletal maturity. Besides a low rejection rate, the method also showed a very good agreement between left- and right-hand assessment and two repeated measurements of the left-hand radiograph. The excellent agreement of the repeated measurement of one radiograph is to be expected, whereas BoneXpert is

an automated computer technique. Other methods used to determine reliability, such as analysis of two radiographs of the same hand of the same patient at one time point, could not be performed, because these radiographs were not available. Bone maturation and cBMD were found to be impaired, as was expected for this group of JIA patients.[198 199 210] A regression analysis showed that delayed bone age was associated with glucocorticoid use and that lower BHI was associated with male gender. The association between delayed bone age and glucocorticoid use was not unexpected, as numerous studies have shown that glucocorticoid use may slow longitudinal bone growth and growth plate senescence.[152 213] In other earlier studies, not only bone age but also impaired BMD has been associated with the use of glucocorticoids.[199 214 215] In the present study, this was not the case; the only variable in the regression analysis significantly associated with cBMD was male gender. The lack of association between glucocorticoid use and cBMD could be due to the broad definition of glucocorticoid use (that is, cumulative dose was not taken into account) and the relatively small size of our study population. On the other hand, several randomized trials in adults with rheumatoid arthritis have shown that glucocorticoids can decelerate the loss of hand BMD.[216 217] Although rheumatoid arthritis and JIA are two different entities, a similar protective effect of glucocorticoids on hand BMD may have played a role in our population. The association with male gender is less easy to interpret. It was previously shown that differences exist between healthy boys and girls in BMD of the forearm, with boys having higher BMD of the forearm than girls.[218] This difference is not associated with body mass index, but is likely to be associated with other factors. The same group also found an association between physical activity and BMD of the forearm, combined with the finding that boys are more physically active than girls.[219] The difference in BHI between boys and girls in the current studies might therefore be explained by low physical activity due to disease activity and by boys being relatively less physically active compared to their healthy peers than girls. The link between physical activity and lower cortical thickness of the forearm was also hinted at in a study in pediatric Crohn's disease patients. In that study, a lower cortical thickness was also found in boys, which improved with treatment, possibly because patients also increased their daily physical activities with their response to treatment.[220]

The BoneXpert method is used to measure bone age and BHI. With respect to bone age, the method can be considered feasible for future use in multicenter or longitudinal follow-up studies in JIA patients, because of its easy use, high precision and small differences between left- and right-hand radiographs.[204] Besides its application in research, the BoneXpert method can also potentially be of use in clinical practice. The automatic determination of bone age and cBMD is less costly than other methods and is time-saving

for both pediatric rheumatologists and radiologists. Moreover, only one hand—either right or left—needs to be analyzed, which increases the feasibility of use in daily practice (unless there is an extreme clinical discrepancy between left and right).

The other major outcome variable, the BHI, needs more validation studies before it can be used in research and clinical practice. The DXR method for the assessment of cBMD, used by BoneXpert, has been compared to DXA in several patient groups, including patients with inflammatory bowel disease.[221] In these patients, the correlation between DXR and DXA was found to be moderate to good. In JIA patients, however, cBMD of the hand may be influenced by local inflammation, possibly resulting in a lower correlation with generalized BMD, as shown in adult patients with rheumatoid arthritis.[222] If BHI can be used as a proxy for generalized BMD in JIA patients, further validation in this population is needed, including a comparison with other BMD measurement techniques. This is complicated by the fact that there are different methods used to determine BMD without consensus on the gold standard, although DXA is the most widely utilized technique.

Limitations

This study is limited by its observational design and the very specific population derived from the ABC register. These factors introduce a selection bias, which limits generalization to the full JIA population. However, patients included in the ABC register are considered to be the most severely affected patients because of their eligibility for biologic treatment; therefore, these patients are most likely to have structural bone damage. It can be assumed that if the BoneXpert method can be applied in these patients, it can be used in all JIA patients. Most radiographs used in this study were digital; however, some conventional radiographs were included. BoneXpert works less well with these digitized images, as demonstrated by the two radiographs that were rejected by the program. Given the widespread use of digital radiology throughout Europe, this will not be a problem in future studies.

CONCLUSIONS

To our knowledge, this study is the first in which the BoneXpert automated determination of bone age and cBMD has been evaluated in JIA patients. The method proved feasible and easy to use, even in severely affected JIA patients, provided that radiographs were of reasonable quality and patients were within the age ranges of the BoneXpert program. This method can be implemented in clinical practice for the determination of bone age in JIA patients. It needs further validation for the determination of bone health, including comparison with existing methods for the determination of BMD.

Chapter 4.3 **Bone health of patients with JIA: a comparison between DXA and BoneXpert**

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Charlotte M. Nusman*, Janneke Anink*, Marieke H. Otten, et al. Bone health of patients with juvenile idiopathic arthritis: a comparison between DXA and digital radiogrammetry

ABSTRACT

Objectives. Juvenile idiopathic arthritis (JIA) affects bone mineral density (BMD). Dual-energy X-ray absorptiometry (DXA) is the most widely used technique to determine BMD. BoneXpert is a new and feasible method for automatic determination of cortical BMD on hand radiographs. This study aimed to compare BoneXpert and DXA in the assessment of BMD in JIA patients.

Methods. Thirty-five JIA patients with available DXA and hand radiograph within the same time period were included from the Dutch Arthritis and Biologicals in Children register. Outcome measures for BMD were Bone Health Index from BoneXpert and BMD total body, BMD lumbar spine and Bone Mineral Apparent Density from DXA. All measures were transformed to Z-scores. Correlations were assessed with Pearson correlation coefficients.

Results. Median age of the patients (60% female) was 11.7 years. Pearson correlation coefficient was significant for the absolute scores: 0.568-0.770 ($p<0.001$). No significant correlation was found between the Z-scores of DXA and BoneXpert.

Conclusions. The BMD assessment from the BoneXpert method was correlated to DXA measures in a cohort of JIA patients, although only in absolute scores. Future steps for implementation of BoneXpert in clinical practice include evaluation of responsiveness to change, predictive value and comparison with other imaging techniques.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an umbrella term that encompasses all forms of arthritis of unknown aetiology that begin before the age of 16 years and persist for more than 6 weeks.[1] Chronic inflammatory activity in JIA affects the bone, possibly resulting in growth abnormalities and decreased bone mineral density (BMD). Low physical activity, chronic exposure to inflammatory cytokines and glucocorticoid therapy all result in a high risk for osteoporosis. Monitoring the bone status of JIA patients is therefore important for the prevention of fractures and osteoporosis at later age.[199] The finding of impaired bone status can lead to preventive actions (e.g. calcium or vitamin D suppletion, physical therapy) or treatment with bisphosphonates in the more severe cases.[223]

The most widely used technique for the assessment of bone mineral density in paediatric patients is dual–energy X-ray absorptiometry (DXA).[201] Recently however an automated method for the evaluation of bone age and BMD has become available, which makes use of hand radiographs.[202] This BoneXpert method is based on digital X-ray radiogrammetry (DXR) and adjusts radiogrammetric measurement of cortical BMD for the automated determined bone age. Advantages of the BoneXpert method include the availability of normative data, low costs, and low effective radiation dose.[205] Additionally, the method proved to be easy-to-use and feasible in the JIA population.[224] Besides a study in children with inflammatory bowel disease (IBD) showing moderate correlations between DXR and DXA, a comparison of DXR with DXA has never been performed in paediatric populations.[221] To be able to use this new method in clinical practice, its place in the framework of existing techniques for the assessment of BMD has to be determined. Therefore the aim of this study was to compare BoneXpert and DXA in the assessment of BMD in JIA patients.

MATERIALS AND METHODS

Patients

Patients were sampled from the Dutch Arthritis and Biologicals in Children (ABC) register. We selected patients included in the ABC register between 2003 and 2012, who were treated in the Erasmus MC Sophia Children's Hospital. These patients were evaluated for BMD by DXA and had conventional radiographs from their hands taken within the same five month period (preferably as close as possible). Patients had to be older than 4 years (the lower limit of Z-scores available for BMD measures) and younger than the upper limits of the reliability range of the BoneXpert method (i.e. 17 years for boys and 15 years for girls).

Clinical data collection

The ABC register aimed to prospectively include all Dutch JIA patients that started treatment with biologic agents since 1999, when the first biologic (etanercept) was approved for the treatment of JIA. The study protocol was approved by the Medical Ethics Committee at Erasmus MC in Rotterdam. Informed consent was obtained from all parents and from patients older than 12 years of age. In the ABC register, demographic data and disease characteristics are collected, including longitudinal data on medication use and disease activity.[40]

BoneXpert

Radiographs of the complete left and right hand and wrists were analysed using the standalone Windows product of BoneXpert (BoneXpert, Version 2.1.0.12, Visiana, Holte, Denmark). The BoneXpert outcome variable of interest was the Bone Health index (BHI).[202] BHI is based on the cortical thickness (T) of the three middle metacarpals. In the construction of BHI, also metacarpal width (W) and length (L) are incorporated to compensate for the high variation in stature of growing children, as expressed in the following formula: $BHI=\pi\ T\ (1 - T/W) / (LW)^{0.33}$.

The BoneXpert method also automatically compares BHI to a Caucasian reference population with the same sex and bone age, and expresses it as a Z-score. Additionally the bone age (based on Greulich and Pyle) and the Z-score of bone age were measured.[202 205] The mean BHI of the right and left hand was analysed, unless only one hand radiograph was available (6 cases). The agreement between right and left hand BoneXpert measurement in JIA patients is very good.[224]

DXA

A DXA scan (Lunar Prodigy, GE, USA) was used to automatically measure BMD of the total body (BMD_{TB}) and the lumbar spine (BMD_{LS}), expressed in g/cm^2. DXA measures areal BMD, based on the density of the cortical and the trabecular bone combined, in contrast to BoneXpert, which only measures BMD of the cortical bone. The Bone Mineral Apparent Density (BMAD) of the lumbar spine was calculated according to the following formula: BMD of L2-L4 $\times$ [4 / ($\pi \times$ width)], expressed in g/cm^3, in which width is the average width of L2-L4.[225] BMAD is used to correct for differences in size of the vertebral bodies. An experience reader assessed the width of the lumbar vertebral bodies on the scans. When there was doubt about the width of lumbar vertebral bodies, another reader was consulted and consensus was reached. BMD_{LS}, BMD_{TB} and BMAD

were compared to a Caucasian reference population from Rotterdam and expressed as Z-scores.[226]

Statistical analysis

Correlations between BMD measurements by DXA and BoneXpert were assessed with Pearson correlation coefficients. To determine whether the BMD measurements differed significantly from the reference population, one sample t-tests were used. A p-value of <0.05 was considered significant. Linear regression was used to investigate whether the relationship between DXA and BoneXpert measurements was influenced by body mass index (BMI), bone age or corticosteroid use (defined as ever versus never use). With DXA Z-scores as a reference, sensitivity, specificity and predictive values were calculated to describe discriminative properties of BoneXpert in distinguishing impaired (<-2SD) from normal bone status. Descriptive statistics are reported as absolute values, mean with standard deviation or median with interquartile range. For all analyses IBM SPSS Statistics for Windows version 21.0 was used (Armonk, NY: IBM Corp.).

RESULTS

Patient characteristics

Patient and disease characteristics of the patients included in this study are shown in Table 1. The systemic JIA category is highly represented in our patient sample (31%). Systemic JIA patients are often treated with high dose systemic corticosteroids, are therefore more likely to develop impaired BMD and often had a DXA scan. Mean BMD measurements by both DXA and BoneXpert were significantly impaired compared to the normal population.

Table 1 Patient characteristics

Characteristic	n=35
Female gender, n (%)	21 (60)
BMI in kg/m^2, mean (SD)	19.2 (±3.9)
Age at onset of JIA in years, median (IQR)	6.0 (3.4-9.8)
JIA category, n (%)	
Systemic JIA	11 (31)
Polyarticular RF positive JIA	3 (9)
Polyarticular RF negative JIA	11 (31)

Oligoarticular extended JIA	7 (20)
Psoriatic JIA	3 (9)
Wrist and/or hand involvement, n (%)	33 (94)
Ever use of corticosteroids, n (%)	30 (86)
Disease duration at radiograph in years, median (IQR)	4.1 (1.8-8.0)
Age at radiograph in years, median (IQR)	11.7 (9.3-14.1)
Z-score bone age in years, mean (SD)	-0.4 (±1.5)
Z-score BMD_{TB}, mean (SD)	-0.7 (±1.3)**
Z-score BMD_{LS}, mean (SD)	-0.7 (±1.1)**
Z-score BMAD, mean (SD)	-0.4 (±1.1)*
Z-score BHI, mean (SD)	-1.1 (±1.2)**
Time between hand radiograph and DXA in months, median (IQR)	0.1 (0.0-0.8)

IQR=interquartile range; JIA=juvenile idiopathic arthritis; BMD_{TB}=total body bone mineral density; BMD_{LS}=lumbar spine bone mineral density; BMAD=bone mineral apparent density; BHI=bone health index; DXA=dual-energy X-ray absorptiometry

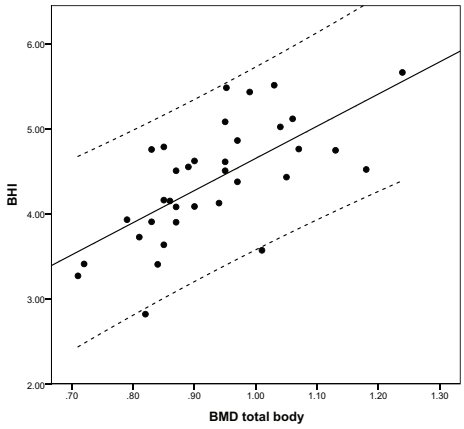
* p-value <0.05 on one sample t-test with test value 0

** p-value <0.01 on one sample t-test with test value 0

Correlation between DXA and BoneXpert

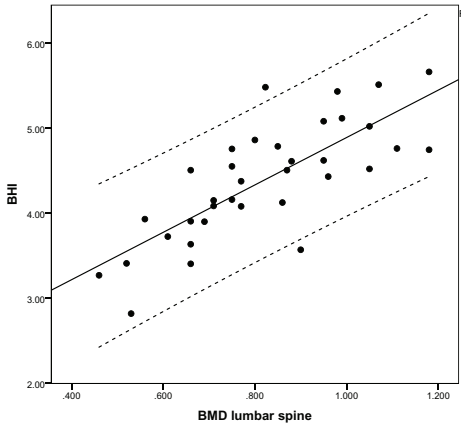
Pearson correlation coefficients were calculated between absolute values and Z-scores of BHI and the BMD measurements by DXA. BHI was significantly correlated to all DXA measurements. The Pearson correlation coefficient was 0.568 ($p<0.001$) for BMAD vs BHI, 0.665 ($p<0.001$) for BMD_{TB} vs BHI, and 0.770 ($p<0.001$) for BMD_{LS} vs BHI. Correlation coefficients were lower and not significant for Z-scores of BHI and DXA measurements. The Pearson correlation coefficients for DXA measurements with Z-score BHI were: 0.263 ($p=0.127$) for Z-score BMAD, 0.137 ($p=0.433$) for Z-score BMD_{TB}, 0.247 ($p=0.153$) for Z-score BMD_{LS}. The correlations between the BoneXpert and DXA for both the absolute values and Z-scores are shown in Figure 1. In a multivariate linear regression, the relationship between Z-score BMAD and Z-score BHI was not significantly influenced by BMI, bone age or corticosteroid use (ever versus never use).

A



R^2 Linear = 0.442

B



R^2 Linear = 0.593

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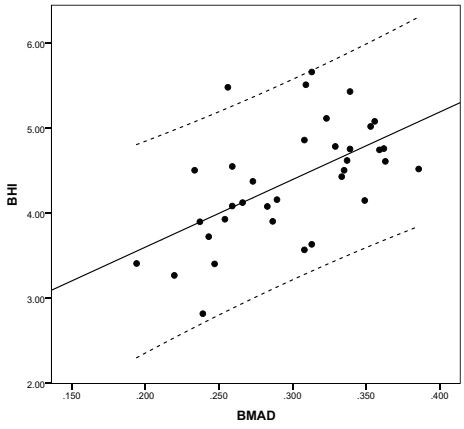

R^2 Linear = 0.323

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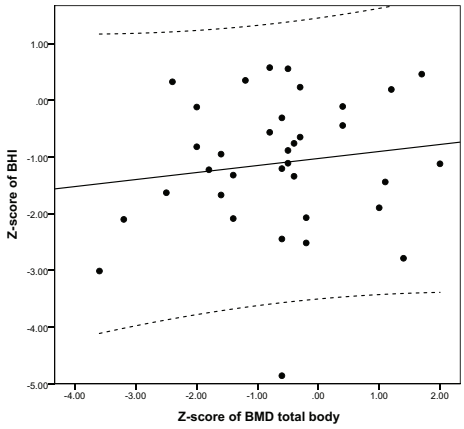
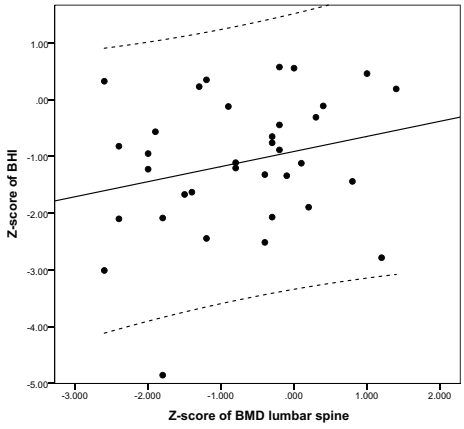


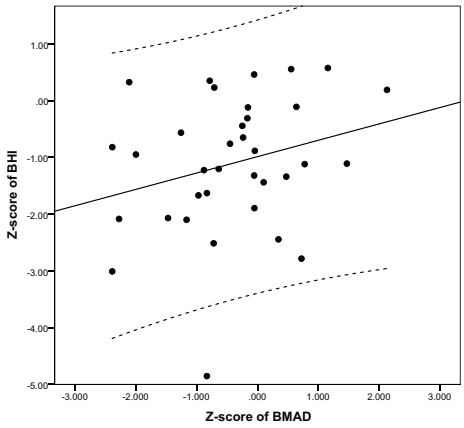
R^2 Linear = 0.019

E



R^2 Linear = 0.061

F



R^2 Linear = 0.069

Figure 1 Correlation between BoneXpert and DXA measures for BMD for both absolute scores (a-c) and Z-scores (d-f) in 35 JIA patients

Agreement between DXA and BoneXpert

For treatment purposes it is most important to identify patients deviating more than 2 standard deviations (SD) from the normal population. We categorized patients according to this criterion and compared how patients were classified according to DXA (BMAD) and BoneXpert. The results are shown in Table 2. According to DXA (BMAD), 5 patients had severely impaired BMD (14%) and according to BoneXpert, BMD was severely impaired in 8 patients (23%). Taking DXA (BMAD) as a reference, BoneXpert had a sensitivity of 40% and a specificity of 80%. A positive test for impaired BMD on BoneXpert resulted in a positive test on DXA in 25% of cases. The negative predictive value was much higher (90%).

Table 2 Classification of BoneXpert and DXA (BMAD) of patients with impaired bone status (scoring ≤-2SD) on either method

	BMAD impaired	BMAD not impaired	Total
BHI impaired	2	6	8
BHI not impaired	3	24	27
Total	5	30	35

BHI=bone health index; BMAD=bone mineral apparent density

DISCUSSION

In this study we compared DXA and BoneXpert for the assessment of BMD in JIA patients. Hand BMD measured by BoneXpert and BMD of the lumbar spine measured by DXA correlated well on absolute scores. However, to properly interpret the values found by both BoneXpert and DXA in this paediatric population, one needs to calculate Z-scores, in which the values are compared to a reference population matched on sex and (bone) age. The Z-scores derived from DXA and BoneXpert measurements did not show any significant correlation.

BoneXpert is a new method, which has the advantage of calculating a Z-score of the BHI based on a reference population matched for sex and bone age. It has never before been compared to DXA measurements in a JIA population. In previous studies however, the DXR method, which BoneXpert applies to derive the BHI, has been compared to DXA. These studies found moderate to good correlations for the absolute values derived from DXA and DXR in both adult and paediatric populations (Table 3).[221 222 227-232] Only one study also compared Z-scores of DXR and DXA (BMD_{LS}) based on a sex and age matched population in 26 children with IBD. This correlation was lower than those found for the absolute values, but still moderate (r=0.58).[221]

Table 3 Studies reporting on the correlation between the DXR BMD and a DXA BMD measurement.

Author (year)	Disease	n	DXA variable	Correlation coefficient	p-value
Adults					
Bottcher (2004)[222]	RA	106	BMD_{LS}	r=0.45	<0.01
Desai (2010)[227]	RA	138	BMD_{LS}	β=0.45	0.004
Forsblad-d'Elia (2011)[228]	RA	75	BMD_{LS}	r=0.52	<0.001
Özçakar (2005)[229]	HIV	27	BMD_{LS}	r=0.60	≤0.01
Rosholm (2001)[230]	Healthy	416	BMD_{LS}	r=0.62	<0.0001
Ward (2003)[232]	Various	154	BMD_{LS}	r=0.56	<0.001
	Children				
van Rijn (2006)[231]	ALL	41	BMD_{LS}	r=0.760-0.853	<0.01
			BMD_{TB}	r=0.806-0.878	<0.01
			BMAD	r=0.666-0.682	<0.01
	GHD	26	BMD_{LS}	r=0.760-0.779	<0.01
			BMD_{TB}	r=0.734-0.760	<0.01
			BMAD	r=0.301-0.414	>0.01
Mentzel (2006)[221]	IBD	26	BMD_{LS}	r=0.78	<0.01
			Z-score BMD_{LS}†	r=0.58	<0.01

† correlation with Z-score DXR-BMD. DXR BMD=digital x-ray radiogrammetry bone mineral density; DXA BMD=dual energy x-ray absorptiometry bone mineral density; r=correlation coefficient; β=beta coefficient; RA=rheumatoid arthritis; BMDLS=bone mineral density lumbar spine; BMDTB=bone mineral density total body; BMAD=bone mineral apparent density; HIV=human immunodeficiency virus; ALL=acute lymphoblastic leukaemia; GHD=growth hormone deficiency.

There may be several explanations for the lack of correlation between the Z-scores derived from DXA and BoneXpert. Firstly, the Z-scores of both measurements are based on different reference populations. The BMAD Z-score derived from DXA, which is first corrected for vertebral size, is sex and age specific. The BHI Z-score derived from BoneXpert is based on a reference population which is sex specific, but instead of age uses bone age to match patients on. The bone age of our cohort was impaired, which may result in difference in these two Z-scores. Another difficulty may lie in the components of the bone on which the two modalities base their BMD measurement. DXA determines BMD based on a measurement of trabecular and cortical bone, whilst the BoneXpert measurement is based on only cortical bone. Trabecular and cortical bone respond differently to stimuli like chronic

inflammation, glucocorticoid treatment and low physical activity.[233 234] Secondly, there is a difference in location for the BMD measurement, as BoneXpert uses the hand and DXA uses the lumbar spine. This is important, because like in RA, BMD in JIA may be affected in two ways.[235 236] There may be generalized bone loss due to systemic influences of chronic inflammation and glucocorticoid use. Additionally, there may be a periarticular effect of local inflammation, functional disability and medication use. In the present study, we could not investigate the effects of local inflammation (arthritis of the wrist) and corticosteroid use, because the majority of our patients were exposed to both risk factors.

Aside from the discussion on the comparability of DXA and BoneXpert, an important point of debate is whether DXA is the best technique to assess BMD, especially in the paediatric population. First of all, variations in body composition, which occur commonly in the growing child, cause inaccuracies in BMD measurement by DXA.[237 238] Secondly, although the BMAD tries to correct for variations in vertebral body size by taking the width of the vertebrae into account, it remains an estimation based on a two-dimensional measurement and does not fully capture true volumetric BMD.[239] This may especially cause imprecise estimates of BMD in a paediatric population like the JIA cohort in the present study, in which patients may have variations in vertebral body size due to physiological and pathological changes (e.g. growth and impaired bone maturation).

A method that does measure true volumetric BMD is (peripheral) quantitative computed tomography ((p)QCT). It is considered to be superior to DXA in its accuracy for BMD measurement.[201 240] Absolute scores and Z-scores of DXA and pQCT were weak to moderately correlated in children with JIA.[241-243] In light of these correlations, it is hard to appreciate the place of BoneXpert in the spectrum of BMD assessment techniques. A comparison of BoneXpert to pQCT for the assessment of both generalized and periarticular bone loss would therefore be worthwhile. Disadvantages of (p)QCT include its high radiation exposure, costs and availability, which make its use in children less desirable.

In the current study only DXA measurements were available for comparison with BoneXpert. Taking DXA as a reference standard, BoneXpert did not identify patients with clinically important deviations in BMD incorrectly. It did miss some patients with an impaired bone status according to DXA. However, to truly evaluate misclassification of clinically relevant impaired bone status, clinical factors like the fracture status would also have to be taken into account. Overall, measuring BMD by any method preferably serves as a tool to determine whether further assessment of risk factors for impaired bone status (e.g. vitamin D levels, calcium intake or physical activity) is warranted.

This is the first study to compare DXA and BoneXpert for the assessment of BMD in JIA

patients. It was limited by the small sample size, and the cross sectional nature of the data. In conclusion, the BoneXpert method was correlated to DXA, although only in absolute scores. The use of BoneXpert for the assessment of BMD in JIA patients is hampered by the complicated concept of measuring bone status in children in general and effects of chronic inflammation and medication use on different modes of BMD in JIA patients specifically. Future practical steps to be taken for the implementation of BoneXpert in clinical practice include the evaluation of its responsiveness to change and predictive value for clinically relevant impaired bone status. Additionally, if possible, BoneXpert should be compared with (p)QCT, to elucidate on its role in identifying both generalized and periarticular BMD.

Chapter 4.4 **MRP8/14 serum levels as predictor of response to starting and stopping TNF-inhibitors in JIA**

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Submitted as:
Janneke Anink, Lisette W.A. van Suijlekom-Smit, Marieke H. Otten, et al. MRP8/14 serum levels as predictor of response to starting and stopping anti-TNF treatment for juvenile idiopathic arthritis

ABSTRACT

Objectives. Approximately 30% of juvenile idiopathic arthritis (JIA) patients fail to respond to anti-TNF treatment. When clinical remission is induced, some patients relapse after treatment has been stopped. We tested the predictive value of MRP8/14 serum levels to identify responders to treatment and relapse after discontinuation of therapy.

Methods. Samples from 88 non-systemic JIA patients who started and 26 patients who discontinued TNF-blockers were analysed. MRP8/14 serum levels were measured by an in-house MRP8/14 ELISA and by Bühlmann MRP8/14 Calprotectin ELISA at start of anti-TNF treatment, within 6 months after start and at time of discontinuation of etanercept in clinical remission. Patients were categorized into responders (ACRpedi≥50 and/or inactive disease) and non-responders (ACRpedi<50) within six months after start, response was evaluated by change in JADAS-10. Disease activity was assessed within six months after discontinuation.

Results. Baseline MRP8/14 levels were higher in responders (median MRP8/14 of 1466 ng/ml (IQR 1045-3170)) compared to non-responders (median MRP8/14 of 812 (IQR 570-1178), p<0.001). Levels rapidly decreased after start of treatment only in responders (p<0.001). JADAS-10 disease activity was significantly correlated to MRP8/14 levels (Spearman's rho: 0.4, p=0.03). Patients who flared within 6 months after treatment discontinuation had higher MRP8/14 levels (p=0.031, median 1025 ng/ml (IQR 588-1288 ng/ml)) compared to patients with stable remission (505 ng/ml (IQR 346-778 ng/ml)). Data were confirmed by the Bühlmann ELISA with high reproducibility but different overall levels.

Conclusions. High levels of baseline MRP8/14 are associated with a good response to anti-TNF treatment, whereas elevated MRP8/14 levels at time of discontinuation of etanercept are associated with a higher chance to flare.

INTRODUCTION

Addition of biologic agents for treatment of juvenile idiopathic arthritis (JIA) has brought the treatment goal of inactive disease into reach even for JIA patients not responding to conventional disease modifying anti-rheumatic drugs (DMARDs). However, for unknown reasons, this treatment goal is still not achieved in 30-40% of patients treated with a biologic agent.[25 39 49] Several clinical parameters have been found to be associated with response to etanercept (a TNF-alpha inhibitor and the first biologic to be approved for the treatment of JIA).[29 244] These include patient characteristics, such as age and gender, as well as characteristics of the disease, such as the number of active joints, the extent of disability and the disease duration. However, these clinical characteristics in themselves are not sufficient to guide treatment decisions. A more tailored approach to drug choice, based upon use of validated biomarkers in combination with clinical parameters, could facilitate early remission induction for more children. Measurement of serum inflammatory proteins before starting treatment with a biologic agent may be valuable to separate children with a high chance of good response from poor- or non-responders. In addition, biomarkers could be of help in identifying patients in clinical remission who can successfully discontinue treatment. The myeloid related protein (MRP) complex 8/14 (S100A8/9, also known as calprotectin) is released from activated monocytes and phagocytes. MRP8/14 is a ligand to Toll-like receptor 4 (TLR-4), has a proinflammatory effect on phagocytes and endothelial cells[245] and is an important factor in mediating osteoclastic bone destruction in experimental arthritis.[246] MRP8/14 serum level correlates with disease activity in JIA patients[247], can be used to identify subclinical disease activity, and is associated with flares in JIA patients who were in clinical remission on MTX.[248 249] In addition, this biomarker correlates closely to the response to treatment in patients with systemic JIA[33] and is able to predict a good response to MTX in a subset of non-systemic JIA patients.[250]

Whether MRP8/14 is also associated with response to TNF-alpha inhibitors in non-systemic JIA patients or can predict flares after discontinuation of etanercept after successful treatment, when clinical remission is achieved, is unknown. Therefore, in the present study we prospectively evaluated the relationship between the clinical course of JIA after start of anti-TNF treatment and after discontinuation of etanercept and the corresponding serum levels of MRP8/14.

PATIENTS AND METHODS

Study population

Serum samples were included from non-systemic biologic naive JIA patients starting either

etanercept or adalimumab included in the Dutch Arthritis and Biologicals in Children (ABC) Register (n=68), German Registry for Biologics in Paediatric Rheumatology (BIKER) (n=12) or Childhood Arthritis Response to Medication Study (CHARMS) from the United Kingdom (n=8). Additionally, samples at discontinuation of etanercept in remission were collected (26 patients (ABC register (n=8), BIKER register (n=18)). Patients fulfilled the International League of Associations for Rheumatology (ILAR) criteria for the diagnosis of juvenile idiopathic arthritis.[1] Patients diagnosed with systemic JIA were described elsewhere.[33] The ABC register is a multicentre prospective observational study that aimed to include all JIA patients in the Netherlands who initiated biologic agents. The study protocol was approved by the Medical Ethics Committee at Erasmus MC Rotterdam and by all participating hospitals.[25] The German BIKER register was founded with the same objective, after approval by the ethics committee of the University Halle.[49] The CHARMS study included JIA patients at the start of treatment with new disease-modifying medication for active arthritis.[250] In all three studies patient and disease characteristics were recorded at start of biologic treatment. Changes in disease activity, medication use and adverse events were thereafter prospectively followed up. These included the JIA core set variables: physician's global assessment of disease activity on a visual analogue scale (VAS) (range 0-10 cm, 0 best score), Childhood Health Assessment Questionnaire (CHAQ) (range 0-3, 0 best score) by patients/parents, the global assessment of wellbeing VAS, number of joints with active arthritis and joints with limited motion and erythrocyte sedimentation rate (ESR). Additionally, pain was assessed using a VAS.

Response to treatment, inactive disease and flare

The effect of treatment was assessed using the ACRpedi 30, 50 and 70 response criteria.[44] A modified definition for inactive disease was used and defined as no active arthritis, no systemic features, no uveitis, normal ESR (≤20 mm/h), and physician's global assessment of disease activity indicating no disease activity (defined as a score ≤10 mm).[123] Patients were divided into responders (who achieved ACRpedi50, ACRpedi70 or inactive disease) and non-responders (patients with no response or an ACRpedi30 response) within 6 months after start of treatment. Additionally, response to treatment was evaluated using the change on the continuous JADAS-10 score, a composite score based on four of the disease activity variables.[23]

Patients who discontinued treatment were all in remission on medication (defined as a period of ≥ 6 months of continuous inactive disease).[45] For the evaluation of the association between MRP 8/14 levels at discontinuation and flaring after discontinuation, we defined

flare based on a combination of previously proposed flare definitions.[128 251] A flare was defined as having at least three of the following: a physician or patient VAS ≥ 20 mm, ≥ 1 active joints, any worsening on the CHAQ and ≥30% worsening on ESR and limited joints.

Determination of MRP8/14 serum levels

Serum levels of MRP8/14 complexes were determined by enzyme-linked immunosorbent assay (ELISA) system. For comparison with earlier studies, internal control sera were used as a reference in all ELISA studies. Additionally, the MRP8/14 levels were measured using the commercially available Bühlmann MRP8/14 Calprotectin ELISA (Bühlmann Laboratories) to investigate interassay variation. The readers of the assay were blinded for diagnosis and disease activity of the patients. Treating physicians were blinded for the MRP8/14 serum levels.

Statistical analysis

Descriptive statistics are presented as absolute frequencies, as median values and interquartile range (IQR) or as mean and standard deviation (SD) wherever appropriate. To compare categorical characteristics of responders with those of non-responders a chi-square test was used. The Mann-Whitney U test was used for comparison of continuous variables. Correlations between the serum level of MRP8/14 and clinical variables were assessed using Spearman's correlation coefficient. The correlation between the in-house ELISA and the Bühlmann ELISA was assessed using Pearson's correlation coefficient. The Wilcoxon signed rank test was used to analyse differences in MRP8/14 levels at paired time points. Receiver operator characteristic (ROC) analyses were performed to determine the optimal cut-off point in MRP8/14 levels for both assays separately to predict response to treatment and flare within 6 months after treatment discontinuation. The cut-off value was determined using the Youden index,[252] if multiple values were available with a high Youden index, the cut-off value with the highest specificity was chosen.

To assess the association between treatment response and baseline MRP8/14 levels as determined by both ELISA methods, univariable logistic regression models were fitted. To evaluate the relationship between change in disease activity and baseline MRP8/14 serum levels a linear regression model was fitted for change in JADAS-10. Change in JADAS-10 was defined as the difference between the baseline and the follow-up JADAS-10. Multivariable linear models were fitted for change in JADAS-10 to correct for other possible predictor variables and to assess additional value of MRP8/14 in predicting clinical response. These variables were specified beforehand based on pre-existing knowledge of

their relationship with serum-levels of MRP8/14 and/or the response to treatment (age at onset of JIA, baseline JADAS-10, number of previously used DMARDs, gender, baseline CHAQ score, ESR). Additionally, disease duration at baseline was considered as a possible predictor and added to the multivariable models.[76] Missing data were handled using the chained equations multiple imputation command *ice* in Stata. Ten imputed datasets were created. Adalimumab and etanercept patients were compared and due to identical characteristics imputed together. Of the baseline JIA core-set variables (including VAS pain) 3.6% was missing (median of 0 missing values per patient (range 0-3). At the last available follow-up within six months of treatment 9.3% of the JIA core set variables were missing (including VAS pain, median of 0 missing values per patient (range 0-7)). Analyses were performed with IBM SPSS Statistics for Windows Version 21.0, Stata/SE version 13.0 and Prism (v5, Graphpad).

RESULTS

Baseline characteristics

Baseline serum samples were available from 88 non-systemic JIA patients and of these 81 were available to perform both in-house and commercial ELISA. The characteristics of both the patients who started TNF-inhibitors and those who discontinued etanercept are summarized in table 1 in the supplementary files. Median MRP8/14 (ng/ml) in patients who started TNF-inhibiting treatment was 1289 (IQR 795-2809).

MRP8/14 serum levels were significantly correlated to ESR at baseline (Spearman's rho 0.440, $p<0.001$). The presence of rheumatoid factor, CHAQ at baseline, number of active joints and disease activity expressed as JADAS-10 were not correlated with MRP8/14 levels.

Clinical response to treatment

A total of 25% of patients (n=22) did not achieve an ACRpedi50 response or higher and were therefore considered non-responders to treatment. The remaining 66 patients were responders. Of these 66 patients, 46 achieved ACRpedi70, and 31 patients reached a state of inactive disease according to the Wallace criteria. Mean JADAS-10 score at the last available follow-up within 6 months was 5.7 (±5.4).

Baseline characteristics of responders and non-responders are shown in Table 1. No significant differences were found between responders and non-responders.

Table 1 Differences in baseline characteristics between responders and non-responders

Baseline characteristic	Responders (n=66)	Non-responders (n=22)
Female gender, n (%)	48 (73)	18 (82)
Age at onset of JIA in years, median (IQR)	10.0 (4.2-12.3)	9.4 (3.5-13.7)
Disease duration in years, median (IQR)	2.4 (1.1-4.9)	2.3 (0.8-7.7)
JADAS-10, median (IQR)	20 (14-21)	17 (11-22)
CHAQ score, median (IQR)	1.5 (0.7-2.2)	1.3 (0.6-2.0)
Number of active joints, median (IQR)	11 (5-18)	8 (2-16)
ESR in mm/h, median (IQR)	16 (9-28)	12 (7-18)
Number of previously used DMARDs, median (IQR)	1 (1-2)	1 (1-2)

IQR=interquartile range; ESR=erythrocyte sedimentation rate; CHAQ=Child Health Assessment Questionnaire; DMARDs=Disease Modifying Anti-Rheumatic Drugs

MRP8/14 serum levels and response to treatment

Baseline MRP8/14 serum levels were higher in responders (median MRP8/14 of 1466 ng/ml (IQR 1045-3170)) compared to non-responders (median MRP8/14 of 812 (IQR 570-1178), p<0.001) (Figure 1). In a univariable logistic regression this resulted in an OR of 1.5 (95% CI: 1.1-2.1) for achieving at least an ACRpedi 50 response per 500 units of MRP (ng/ml). Baseline MRP8/14 was weakly but significantly correlated with change in JADAS-10 score over three months of treatment (Spearman's rho 0.361, p=0.001).

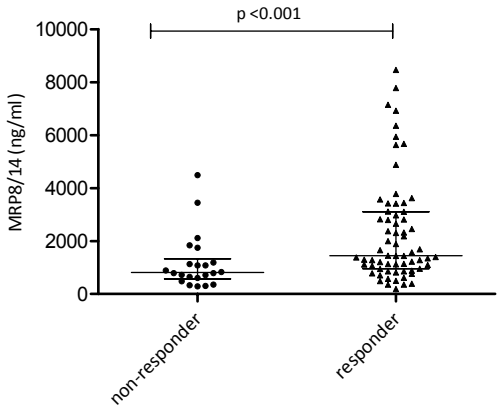

Figure 1 Difference in MRP8/14 between non-responders and responders

Use of MRP8/14 as a prognostic marker for response to treatment

Based on ROC analysis, cut off values were identified for the prediction of response to treatment (ACR pedi50 or higher). Sensitivity, specificity and likelihood ratios are given in table 2.

Table 2 Sensitivity, specificity and likelihood ratios for the determined cut-off value of MRP8/14 predicting response to anti-TNF treatment

Accuracy measure	
Cut-off level MRP8/14 (ng/ml)	1193
Sensitivity	66%
Specificity	81%
Positive likelihood ratio	3.4
Negative likelihood ratio	0.4
Youden index	0.47
AUC	0.76

AUC=area under the curve

Added value of MRP8/14 in prediction of response

Baseline MRP8/14 serum levels were significantly associated with change in JADAS-10 in a linear regression analysis (β=0.636 per 500 unit increase in ng/ml, 95% CI 0.254 to 1.018, p=0.001). Since other factors can also be associated with treatment effect we constructed a multivariable linear regression model with these known factors and subsequently added MRP8/14 to the model. In this multivariable model MRP8/14 was still significantly associated with the change in JADAS-10 (corrected β=0.472 per 500 units increase in ng/ml, 95% CI 0.161 to 0.782, p<0.001). The only other variable significantly associated with the change in JADAS-10 was the baseline JADAS-10 (corrected β=0.678, 95% CI 0.434 to 0.921, p<0.001). The variables in the model without MRP8/14 serum levels explained 50% of the variance in the change in JADAS-10 over three months of treatment (R^2=0.50). Adding MRP8/14 to this model resulted in a slightly better predictive model, with an R^2 of 0.54 (p=0.004).

Change in MRP8/14 levels after treatment

For 43 patients, a follow-up measurement within five months after start of anti-TNF treatment was available, and 14 of these could be categorized as being non-responders.

Treatment with etanercept lowered MRP8/14 serum levels significantly only in responders ($p<0.001$) (Figure 2A), but not in non-responders (Figure 2B). Change in MRP was significantly correlated to change in JADAS10 (Spearman's rho: 0.421, p=0.006).

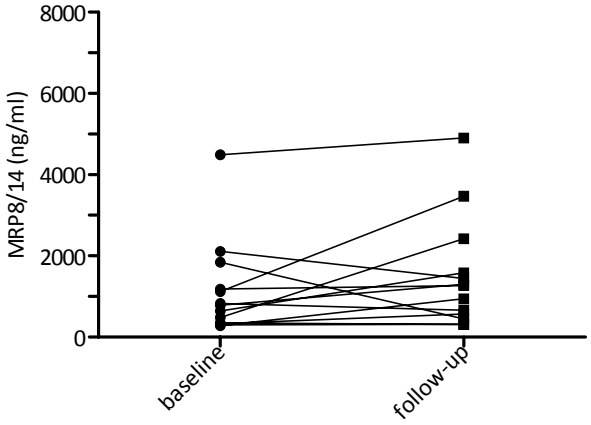

Figure 2A Change in MRP8/14 levels in non-responders

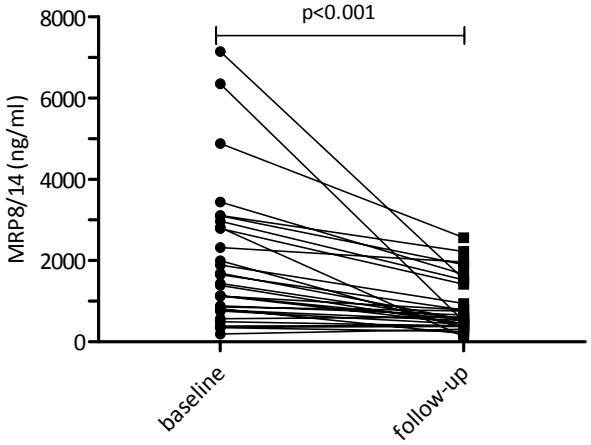

Figure 2B Change in MRP8/14 levels in responders

Association of MRP8/14 level and flare after etanercept withdrawal after successful treatment

Patients who flared within 6 months (n=12) after the discontinuation of etanercept had higher MRP levels at discontinuation than patients who did not flare (n=14) (p=0.031, median 1025 ng/ml (IQR 588-1288 ng/ml) vs. 505 ng/ml (IQR 346-778 ng/ml) figure 3).

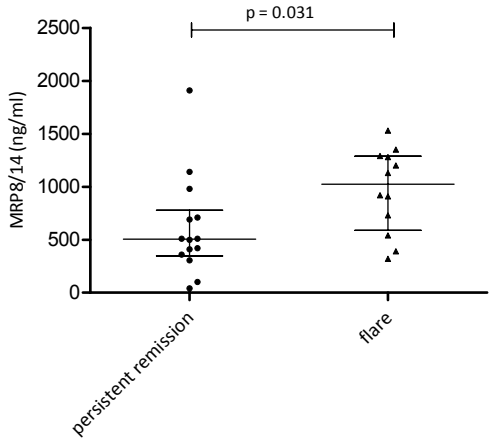

Figure 3A Differences in MRP8/14 between patients with persistent remission and patients who flared after discontinuation of etanercept, median (range)

The cut-off for the prediction of a flare after etanercept withdrawal and the prognostic accuracy are reported in table 3.

Table 3 Sensitivity, specificity and likelihood ratios for the determined cut-off value of MRP8/14 predicting a flare within 6 months

Accuracy measure	
Cut-off level MRP8/14 (ng/ml)	720
Sensitivity	75%
Specificity	79%
Positive likelihood ratio	3.5
Negative likelihood ratio	0.5
Youden index	0.54
AUC (95% CI)	0.75 (0.55 to 0.95)

AUC=area under the curve

Validation for routine use by commercial ELISA

Commercial MRP8/14 ELISAs are available but not validated for use as monitoring tool of anti-TNF therapy. Therefore, we aimed to validate our findings with the commercial Bühlmann MRP8/14 Calprotectin ELISA to make MRP8/14 as marker for anti-TNF therapy widely available. The measurements by the in-house ELISA correlated very well with those from the Bühlmann ELISA (Pearson's rho 0.902, $p<0.001$). Although MRP8/14 levels appeared to be 3-4 fold higher when they were measured with the Bühlmann ELISA, the associations between MRP8/14 and response, on both the achievement of ACRpedi 50 or higher and on the change in JADAS-10 were comparable.

For predicting response to anti-TNF treatment, the in-house ELISA and the Bühlmann ELISA had the same accuracy. The two methods differed to some extent with regard to their accuracy for predicting a flare/ persistent remission after discontinuation of etanercept in remission. Using the cut-off values we found, a prediction of a flare by the in-house ELISA was marginally more accurate than by the Bühlmann ELISA. The Bühlmann ELISA had higher sensitivity and lower negative LR and was therefore better at predicting persistent remission in the first 6 months after discontinuation. The exact results for the Bühlmann ELISA can be found in the supplementary files.

DISCUSSION

In this study we show that MRP8/14 can predict response to anti-TNF treatment, although it has little additive value to other clinical factors. Patients who responded to anti-TNF treatment had higher levels of MRP8/14 at start of that treatment than patients who did not respond. Disease activity declined more in patients with higher levels of MRP8/14. In responders, these levels decreased after initiation of treatment, in non-responders MRP8/14 levels were constant. When the disease had become inactive and treatment with etanercept could be stopped, MRP8/14 levels appeared to be higher for patients in whom the disease flared than for patients who did not experience a flare. The prognostic accuracy of the two ELISAs differed slightly. The in-house experimental ELISA performed better on predicting response to treatment and occurrence of flares, while the commercial Bühlmann ELISA predicted non-response and persistent remission after discontinuation more accurately.

In recent years, MRP8/14 has been widely studied as a potential predictor of disease activity and response to treatment in rheumatic and other inflammatory diseases. In rheumatoid arthritis (RA), MRP8/14 could be used as a predictor for response to biologic treatment.[253] In JIA in particular, MRP8/14 levels are highly predictive of disease activity

and of disease flares in systemic JIA.[33] Also in enthesitis related arthritis, a relationship with disease activity exists.[254] In a more heterogeneous group of JIA patients, MRP8/14 levels have been shown to predict response to MTX treatment.[250] The univariable odds ratio for achieving an ACRpedi50 response or higher following MTX treatment [250] is comparable to the odds ratio found in the present study following anti-TNF treatment. Using the same ELISA to measure MRP8/14 levels, the average serum levels of MRP8/14 in that study were higher than in our patients, as were the cut-off points specified. Patients in the present study mostly had MRP8/14 levels comparable to the patients who did not respond to MTX treatment.[250] This is not surprising as failure of MTX treatment is an eligibility criterion for treatment with biologic agents. Therefore there may be a possibility of using MRP8/14 levels to decide which patient is more likely to respond to MTX and which patient may be better off with biologic treatment right away. Unfortunately we did not have MRP8/14 serum levels of our patients at the start of MTX treatment.

Well-established experimental ELISA protocols exist for MRP8/14, however these are not available for use in routine laboratories. We have already demonstrated good performance of the commercially available Bühlmann ELISA kit designed for analysing patient serum samples and the necessity for serial dilution of individual sera to obtain reliable results in the range of MRP8/14 concentrations found during different disease levels of JIA.[255] In addition, the level of MRP8/14 concentrations analysed with the two assays varied substantially. Therefore, a direct comparison of the results obtained with one ELISA with a result from a different assay should not be made. Both methods were equally accurate in predicting response to treatment. We found slight differences in prognostic performance for predicting a flare after discontinuation of teatment in remission, the in-house ELISA being more accurate in predicting a flare and the commercially available Bühlmann ELISA being more accurate in predicting persistent remission.

For a biomarker to be used in informing therapeutic choice, it will have to fulfil certain requirements. It has to be able to predict a certain outcome and this predictive value has to be validated. It has to have additional value on top of other known predictors. Additionally the prediction should have therapeutical consequences. MRP8/14 has shown to be predictive of response to treatment, in both the current as well as previous studies in JIA. Its value added to other predictors however is small. Some of the responders and non-responders to treatment had comparable MRP8/14 serum levels, and sensitivity and specificity were not optimal for any cut-off value, which is in line with the results found in the study by Montcrieffe et al.[250] Because prediction is not perfect, therapeutic decisions cannot only be based on MRP8/14 levels. However, it is unlikely that a single biomarker

will ever be able to perfectly predict response in the heterogeneous pool of JIA patients. MRP8/14 has the advantage that it is a relatively stable protein and easily measurable in serum, in contrast to for instance cytokines such as TNF or IL-1beta. Therefore, MRP8/14 could play a supporting role in response prediction models for response to treatment including clinical as well as laboratory measures, which are under investigation for both JIA and RA.[29 256-260] More importantly, MRP8/14 might be used to objectively monitor disease activity as it has shown to decrease together with disease activity and might be useful as an early marker of response in clinical trials.

For prediction of flares after discontinuation of treatment, MRP8/14 can be used as a prediction tool. MRP8/14 serum levels have already been shown to be predictive of flares after the discontinuation of MTX in JIA patients.[249] We show that this is true to the same extent for stopping etanercept in non-systemic JIA patients after inactive disease has been achieved. Additionally, we found cut-off values comparable to the earlier specified cut-off value for the in-house ELISA, giving an even higher sensitivity and specificity than described in the other cohort.[249 255] The likelihood ratios indicated that this marker could be of value in predicting the likelihood of a flare after stopping of therapy. Still, the cut-off values did not perfectly predict flare or persistent remission after discontinuation. For clinical practice this means that we have to keep searching for additional features that will provide such a perfect prediction.

In conclusion, serum levels of MRP8/14 are associated with response to treatment with etanercept in non-systemic JIA patients. They could be a useful addition to response prediction models in combination with other factors associated with response. MRP8/14 serum levels decrease together with disease activity in responders to etanercept. MRP8/14 serum levels can very well be used to predict flares in patients in clinical remission after cessation of etanercept. They can also be determined using a commercially available ELISA kit when the specific prognostic performance of this kit is kept in mind.

SUPPLEMENTARY FILE – TABLE 1A AND TABLE 1B PATIENT CHARACTERISTICS

Table 1A Characteristics of patients who started anti-TNF treatment

Baseline characteristics	N=88
Female, n (%)	66 (75)
Age at onset JIA in years, median (IQR)	10.0 (3.9-12.3)
Age at start first biological in years, median (IQR)	12.8 (9.9-15.6)
JIA disease duration before start biological in years, median (IQR)	2.3 (0.9-6.0)
ANA positive, n/N (%)	25/76 (33)
RF positive, n/N (%)	13/80 (16)
Category JIA, n (%)	
Polyarticular RF negative	33 (3.8)
Polyarticular RF positive	13 (15)
Oligoarticular extended	24 (27)
Oligoarticular persistent	5 (6)
Psoriatic arthritis	9 (10)
Enthesitis related arthritis	4 (5)
Previously used medications, n (%)	
Systemic prednisone	42 (48)
Methotrexate	85 (97)
DMARD other than MTX	26 (30)
Biological started, n (%)	
Etanercept	81 (92)
Adalimumab	7 (8)
Concomitant co-medication at start biological, n (%)	
Systemic prednisone	25 (28)
Methotrexate	74 (84)
DMARD other than MTX	3 (3)
Disease activity parameters at baseline, median (IQR)	
VAS physician (0-100)	54 (30-68)
CHAQ total (0-3)	1.50 (0.75-2.1)
VAS pain (0-100)	56 (25-72)
VAS wellbeing (0-100)	53 (25-70)
Active joints	10 (5-17)
Limited joints	6 (2-14)
ESR	13 (8-27)
JADAS-10 (0-40), mean (SD)	18 (7)
MRP8/14 measured by in-house ELISA (ng/ml), median (IQR)	1289 (795-2809)
MRP8/14 measured by Bühlmann ELISA (ng/ml), median (IQR)	4763 (2795-8701)

JIA=juvenile idiopathic arthritis, IQR=interquartile range, ANA=anti-nuclear antibodies, RF=rheumatoid factor, DMARD=disease modifying anti-rheumatic drug, MTX=methotrexate, VAS=visual analogue scale, CHAQ=childhood health assessment questionnaire, ESR=erythrocyte sedimentation rate, JADAS=juvenile arthritis disease activity score

Table 1B Characteristics of patients discontinuing etanercept in clinical remission

Baseline characteristics	Flare (n=12)
Female, n (%)	9 (75)
Category JIA, n (%)	
Polyarticular RF negative	6 (50)
Polyarticular RF positive	-
Oligoarticular extended	-
Oligoarticular persistent	3 (25)
Psoriatic arthritis	1 (8)
Enthesitis related arthritis	2 (17)
MTX treatment at time of discontinuation, n (%)	5 (42)
MRP8/14 measured by in-house ELISA (ng/ml), median (IQR)	1025 (588-1288)
MRP8/14 measured by Bühlmann ELISA (ng/ml), median (IQR)	3835 (2146-4806)

JIA=juvenile idiopathic arthritis, IQR=interquartile range, RF=rheumatoid factor, MTX=methotrexate, MRP=myeloid related protein

SUPPLEMENTARY FILE - RESULTS OF BÜHLMANN ELISA

MRP8/14 levels at baseline and response to treatment

MRP8/14 serum levels were significantly correlated to ESR at baseline (Spearman's rho 0.361, p=0.001 (Bühlmann ELISA)). Baseline MRP8/14 serum levels were higher in responders (median in responders was 5556 (IQR 3092-10008)) compared to non-responders (median 2504 (IQR 1292-3950), p<0.001)) (Figure 1).

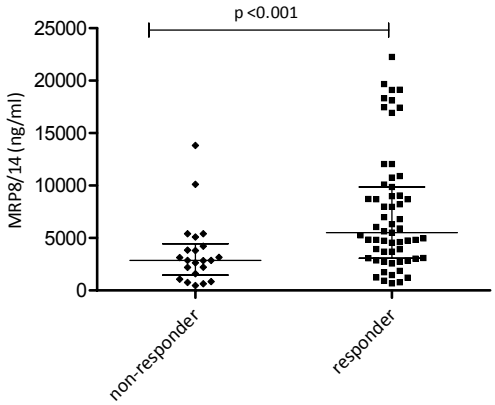

Figure 1 Differences in MRP8/14 between non-responders and responders, Bühlmann ELISA

In a univariable logistic regression this resulted in an OR of 1.2 (95% CI: 1.0-1.3) for achieving at least an ACRpedi 50 response per 500 units of MRP (ng/ml) for the Bühlmann ELISA measurements.

Prediction of response corrected for other variables

Baseline MRP8/14 serum levels were significantly associated with change in JADAS-10 in a univariable linear regression analysis (β=0.245, 95% CI 0.116 to 0.375, p<0.001 for the Bühlmann ELISA). IN the corrected multivariable analysis the corrected β was 0.197 per 500 units increase in ng/ml, 95% CI 0.087 to 0.306, p<0.001. The change in explained variance was identical: 4%.

Use of MRP8/14 as a prognostic marker for response to treatment

The in-house ELISA and the Bühlmann ELISA had the same accuracy for predicting response to anti-TNF treatment, the accuracy of the Bühlmann ELISA is shown in table 2.

Table 2 Sensitivity, specificity and likelihood ratios for the determined cut-off value of MRP8/14 predicting response to anti-TNF treatment, Bühlmann ELISA

Accuracy measure	Bühlmann ELISA
Cut-off level MRP8/14 (ng/ml)	4387
Sensitivity	67%
Specificity	81%
Positive likelihood ratio	3.4
Negative likelihood ratio	0.4
Youden index	0.47
AUC	0.77

AUC=area under the curve

Change in MRP8/14 levels after treatment

Of 34 patients, enough serum was available to determine MRP in the follow-up sample. Of these patients 11 could be categorized as non-responders. Treatment with etanercept lowered MRP8/14 serum levels significantly only in responders (p<0.001 for both ELISAs) (Figure 2A), but not in non-responders (Figure 2B)). Change in MRP was significantly correlated to change in JADAS10 (Spearman's rho: 0.581, p=0.001 (Bühlmann ELISA)).

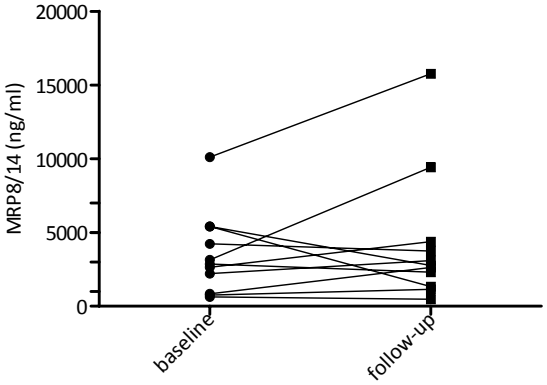

Figure 2A Change in MRP8/14 in non-responders, Bühlmann ELISA

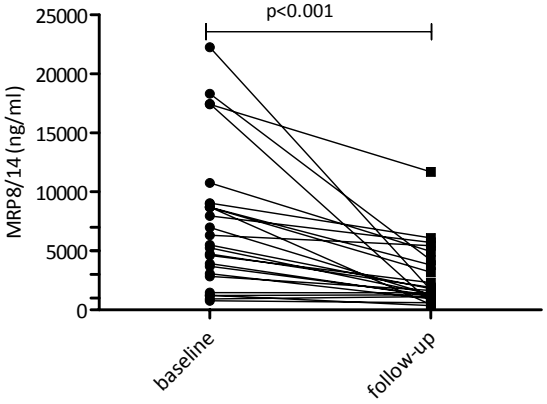

Figure 2B Change in MRP8/14 in responders, Bühlmann ELISA

Association of MRP8/14 level and flare after etanercept withdrawal after successful treatment

Patients who flared within 6 months (n=12) after the discontinuation of etanercept had higher MRP levels at discontinuation than patients who did not flare (n=14) (p=0.013, median 3835 (IQR 2146-4806) vs. 1415 (IQR 1099-863) (Bühlmann ELISA), figure 3).

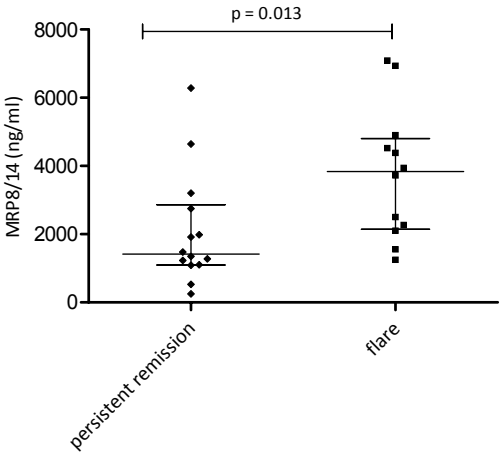

Figure 3 Differences in MRP8/14 between patients with persistent remission and patients who flared after discontinuation of etanercept on the Bühlmann ELISA

Cut-off for the prediction of a flare after etanercept withdrawal plus their prognostic accuracy are given in table 3.

Table 3 Sensitivity, specificity and likelihood ratios for the determined cut-off value of MRP8/14 predicting a flare within 6 months

Accuracy measure	Bühlmann ELISA
Cut-off level MRP8/14 (ng/ml)	2045
Sensitivity	83%
Specificity	71%
Positive likelihood ratio	2.9
Negative likelihood ratio	0.2
Youden index	0.55
AUC (95% CI)	0.79 (0.61 to 0.96)

AUC=area under the curve

Chapter 4.5 **Anti-CarP antibodies in sera of JIA patients**

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LETTER

In juvenile idiopathic arthritis (JIA) patients there is a lack of markers that predict severe disease. Although anticitrullinated protein antibodies (ACPA) have contributed substantially to the understanding of rheumatoid arthritis (RA),[261] their detection in JIA has not been equally useful as incidence rates in JIA patients are low [262] and merely confined to the polyarticular immunoglobulin (Ig)M-rheumatoid factor (RF)-positive category resembling RA. Recently, anticarbamylated protein (anti-CarP) antibodies were detected in 45% of RA patients and importantly also in 16%–20% ACPA-negative patients.[263-265] Within the ACPA-negative patients, anti-CarP antibodies were associated with more severe radiographic progression.[263] Since most JIA patients are ACPA-negative, we investigated whether anti-CarP antibodies are present in the sera of JIA patients and how they are related to ACPA and IgM-RF.

JIA patients from three Dutch sources were included: the *BeSt for Kids trial* (NTR 1574, a treatment strategy study) (n=33), a previously described cohort [266](n=48) and the Arthritis and Biologicals in Children (ABC) register [29](n=153). Healthy controls (n=107) (mean age (range) 11 (2–20)) are stem-cell graft donors. Written informed consent was obtained from all patients and controls. Blood collection and storage are comparable among different cohorts. Cross-sectionally obtained sera from 234 JIA patients at variable time points in disease course were analysed. All International League against Rheumatism JIA categories were included[1] with polyarticular JIA over-represented. Median disease duration at the time of serum collection was 2.3 years (IQR 0.7–6.8) (table 1). Patients' disease characteristics were collected from patient files. Anti-CarP antibodies and ACPA were measured by ELISA as described previously.[263]

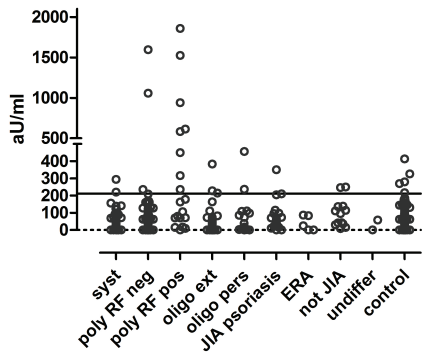
Table 1 Disease characteristics of 234 JIA patients

Characteristics	Number
Gender m/f (%f)	76/158 (67.5%)
Median age (years) (IQR)	12.1 (8.4–16.2)
Median disease duration (IQR)	2.3 (0.7–6.8)
Median age at JIA onset (IQR)	8.8 (3.4–12.4)
ANA-positive at disease onset	64 (27.4%)
Systemic JIA	35 (15.0%)
Polyarticular JIA RF-negative	90 (38.5%)
Polyarticular JIA RF-positive	19 (8.1%)
Oligo-articular JIA extended	41 (17.5%)
Oligo-articular JIA persistent	18 (7.7%)
Juvenile psoriatic arthritis	24 (10.3%)
Enthesitis-related arthritis	5 (2.1%)
Undifferentiated	2 (0.8%)

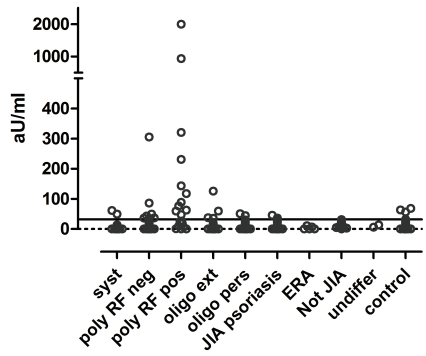
ANA=anti-nuclear antibodies; RF=rheumatoid factor.

We observed that 8.1% (19/234) of the JIA patients were positive for anti-Ca-FCS antibodies versus 4.7% (5/107) of controls (p=0.20); 13.2% (31/234) of patients versus 2.8% (3/107) of controls were positive for anti-Ca-Fib antibodies (p=0.003); 16.7% (39/234) of patients versus 8/107 (7.5%) of controls were positive for at least one anti-CarP antibody (p=0.028); and 11/234 (4.7%) versus 0 of controls (p=0.017) were positive for both anti-CarP reactivities. Both anti-Ca-FCS and anti-Ca-Fib antibodies were predominantly present in polyarticular IgM-RF-positive patients compared with other JIA categories (p<0.0001) (figure 1). Additionally, 53% (8/15) of ACPA-positive patients and 42.1% (8/19) of IgM-RF-positive patients were also positive for anti-CarP antibodies. Importantly, anti-CarP antibodies were also found in ACPA and IgM-RF-negative patients as 57.9% (11/19) of anti-CarP-positive patients were negative for ACPA and 27.3% (3/11) were negative for IgM-RF. In total, nine JIA patients were positive for IgM-RF, ACPA and anti-CarP (Ca-FCS and/or Ca-Fib) antibodies. All triple positive patients were part of the ABC register.

A



B



C

	Anti-CarP-FCS		Anti-CarP-Fib	
	n/total (%)		n/total (%)	
All JIA in total	19/234 (8.1)	NS	31/234 (13.2)	**
Systemic onset JIA	2/35 (5.7)	NS	2/35 (5.7)	NS
Polyarticular RF negative	3/90 (3.3)	NS	9/90 (10.0)	*
Polyarticular RF positive	8/19 (42.1)	**	11/19 (57.9)	**
Oligo articular extended	3/41 (7.3)	NS	4/41 (9.8)	NS
Oligo articular persistent	2/18 (11.1)	NS	2/18 (11.1)	NS
Juvenile Psoriatic Arthritis	1/24 (4.2)	NS	3/24 (12.5)	NS
Enthesitis Related Arthritis	0	NS	0	NS
Undifferentiated	0	NS	0	NS
Controls	5/107 (4.7)		3/107 (2.8)	

Figure 1 IgG anticarbamylated protein (anti-CarP) antibodies are present in juvenile idiopathic arthritis (JIA) sera. A cut-off for positivity (horizontal line) was determined using the mean plus two times the SD of the healthy controls. Antibodies against Ca-FCS (A) and Ca-Fib (B) in the sera of JIA patients and healthy controls are depicted in aU/mL. (C) Results of anti-CarP antibodies: positivity above cut-off per JIA category in absolute number, percentage and significance (NS=not significant, *p<0.05, **p<0.01). FCS=fetal calf serum; RF=rheumatoid factor.

Disease duration at sample collection, anti-nuclear antibodies status or age was not associated with the presence of anti-CarP antibodies. In the second cohort,[266] we did not find an association of anti-CarP positivity with disease activity measured by time-in-active-disease at the time of sampling. Within the ABC register cohort, no association was found

between the presence of anti-CarP antibodies and ACR-Pedi 30 response[44] or reaching inactive disease [123] at 15 months after starting anti-TNF treatment. The cross-sectional nature of these three cohorts did not allow a more in-depth analysis on the association with clinical outcome.

This is the first study showing the presence of anti-CarP antibodies in JIA stimulating future studies on the diagnostic and prognostic value of anti-CarP antibodies in JIA.

Chapter 5. **General discussion**

The management of JIA has developed greatly in the last few decades. The possibility of treatment with synthetic DMARDs early in the disease course and the introduction of biologic therapy significantly improved the prospects of children with JIA. The ABC register has provided a unique opportunity to study the effects of the introduction of biologic treatment in real life. Previous analyses from this register predominantly reported on the effectiveness of etanercept on the disease activity and functional and quality of life outcomes. Since the introduction of etanercept however, a wide range of biologic agents has become available which resulted in a transformation of the management of JIA. This thesis studied the effects of these changes in an observational study design. It investigated both the effectiveness of biologic agents as well as the changes in the prescription behaviour of physicians. It looked into the patient population to which biologic agents are prescribed and examined its effectiveness in patients to whom the drug was prescribed off-label. Additionally part of this thesis is dedicated to the study of new developments in monitoring tools including biomarkers, a patient-reported joint-count and a new method of evaluating bone age and bone density.
In the following chapter the main findings of this thesis are reviewed and discussed in light of current clinical practice. Methodological considerations of this thesis and the study of JIA in general are discussed. Finally, recommendations for future research are given.

THE CHANGING LANDSCAPE OF JIA TREATMENT – FINDINGS AND CLINICAL IMPLICATIONS

Trends in biologic treatment, effectiveness and long term outcome

The efficacy and effectiveness of etanercept were proven in an RCT and numerous observational studies. Because it was the first (and for a long time the only) biologic agent to be approved for the treatment of JIA, etanercept has been studied extensively both in and outside the ABC register.[164] In this thesis, the effectiveness of etanercept was underlined in a long-term follow-up study in which the gain in quality of life after start of treatment appeared to be persistent and disability scores were low, even 8.5 years after treatment began (chapter 2.2). Interestingly, although overall quality of life showed sustained improvement, pain scores worsened since the last measurement. The levels of pain patients indicated did not fully correspond with the low disease activity observed in this study. Chronic pain without corresponding disease activity is a subject that is not clearly understood and deserves attention.[267]
Although we saw that over the course of the study biologic treatment was prescribed earlier

in the disease course (chapter 3.1), half of the patients in the long term follow-up study still had radiological damage in the long run (chapter 2.2). In the majority of these patients, some form of radiological damage had been reported already before the start of etanercept. Patients in the long term follow-up study were mostly patients included in the earlier years of the ABC register. However, it may be worth reconsidering the timing of biologic treatment; some patients may benefit from a start of biologic treatment very early in the disease course, thereby preventing the development of radiological damage.

With the expansion of the biologic armament the experience of physicians with this class of drugs increased (chapter 3.2). Both the increased treatment options as well as the increased experience led to changes in prescription patterns; a wider range of biologic agents was prescribed to more and different kinds of patients.

Between 1999 and 2012, etanercept continued to be the most prescribed biologic agent for non-systemic JIA (chapter 3.1). Although adalimumab had been approved in 2008 for non-systemic JIA, it was still prescribed infrequently and to a specific subset of patients.

Over the course of the study, anakinra became the most prescribed drug for systemic JIA as first biologic treatment (chapter 3.1). With regard to the second biologic treatment, after failure of etanercept, we observed that systemic JIA patients responded well to a switch to anakinra, much better than to a second TNF-inhibiting agent (chapter 3.4). These findings were expected, because of an increasing understanding of the underlying immunological and inflammatory pathways. While non-systemic JIA is regarded as an auto-immune disease with principal abnormalities in the adaptive immune system, systemic JIA is now regarded as an auto-inflammatory disease with principal abnormalities in the innate immune system. These abnormalities result in high circulating levels of, among other pro-inflammatory cytokines, IL-1 and IL-6.[84 85 268]

Because we now regard the inflammatory process underlying systemic JIA to be distinct from non-systemic JIA, with an important role for IL-1, and because it was for long the only IL-1 inhibitor available, anakinra is currently the first choice of biologic treatment for this JIA category in treatment recommendations.[269] It is however not approved by FDA or EMA for this indication. Tocilizumab is approved for systemic JIA, however is at this point regarded as second line biologic treatment for this indication. Off-label use of canakinumab is also regarded as a possible second-line step.[269] For patients with systemic features IL-1 and IL-6 seem the most logical targets. However, there seems to be a distinct group of patients in whom the autoinflammatory start of the disease advances into an autoimmune disease course. For these patients in whom the systemic features subside, but polyarthritis remains, TNF-blockade may be an effective option.[29 151 270 271]

Tocilizumab has now also been approved for the treatment of non-systemic JIA. Its approval was so recent that we could not comment in this thesis on the tocilizumab's effectiveness as either first biologic agent or second-line biologic treatment. It may be worth trying to target IL-6 after the failure of etanercept, as the effectiveness of a second TNF-inhibitor is likely to be reduced, especially when the reason for switching was ineffectiveness of etanercept (chapter 3.4).
During the course of the study, biologic agents were also prescribed to a different kind of patient (chapter 3.1). We observed that biologic agents were no longer only prescribed to patients for whom biologic treatment was originally reserved (polyarticular or systemic course of disease). Also in these oligoarticular persistent JIA patients, who were all refractory to MTX treatment and intra-articular corticosteroid injections, TNF-inhibitors were effective in decreasing disease activity (chapter 2.1). Apparently for some physicians, the number of affected joints was not the most important feature in the decision to treat with a biologic agent. This is in line with current treatment recommendations for JIA, in which other prognostic factors and disease activity indicators are also part of the decision making process.[17] Although these guidelines are a step in the direction of a more personalized treat-to-target regimen, there is room for improvement to fully individualize JIA therapy. For every patient, whether it is a patient fulfilling eligibility criteria or not, the physician has to be aware of the harms and benefits of the treatment that is prescribed. Although it seems that biologic treatment, and particularly etanercept, is safe, very long term effects are still largely unknown. In addition, the medication is relatively expensive. Possible adverse events and costs should always be part of clinical decision making.

Decision making and comparative effectiveness

The decision making process regarding treatment was also subject of research in this thesis. Although new treatment options became available in rapid succession, physicians were still relatively slow in adapting to these new treatment options, especially when the new drug targeted the same cytokine as an older and more well known drug, as is the case with adalimumab and etanercept (chapter 3.1 and chapter 3.2). Physicians indicated that they kept to etanercept because they were less familiar with the (long term) adverse events of adalimumab. Furthermore most physicians prescribed this new drug only to specific patients. They thought adalimumab to be more effective for the JIA category the patient was diagnosed with or for the extra-articular symptoms that accompanied that JIA category, such as uveitis or gastro-intestinal problems (chapter 3.2). Although they base their decisions on ideas about differences in effectiveness, true comparative effectiveness

studies are scarce and guidelines (for instance for uveitis treatment) are largely based on expert opinion.[272] To achieve a higher level of evidence, particularly in this fast changing landscape of biologic treatment, comparative effectiveness studies are urgently needed to support clinical decision making.[273]

Several attempts were made in this thesis to compare different treatments. In these comparisons various methodological challenges were faced. Firstly, switching to another biologic agent after the failure of etanercept proved to be effective in some patients, using drug persistence as a proxy for effectiveness (chapter 3.4). When prescribed as the second TNF-inhibiting treatment after the failure of etanercept, adalimumab and infliximab seemed to be equally effective. Because this was an analysis performed in a real-life database, it was influenced by the prescription behaviour that prevailed at the time, which was again inevitably shaped by the availability of biologic agents within the study period. The drug adherence may very well be affected by the fact that etanercept was the only available drug at the beginning of biologic treatment. The same is true for the second treatment, after which again no other agents may have been available. Correcting for this confounding is difficult, and it is therefore hard to draw any definite conclusions on the comparative effectiveness of the separate TNF-inhibitors after the failure of etanercept.

Physicians have their reasons to treat a specific patient with a specific drug, and this reasoning may also affect the outcome of the patient. The treatment choices of physicians and the resulting confounding by indication resulted in difficulties in the comparison of adalimumab and etanercept as first biologic agent (chapter 3.5). Three types of analyses could not give a definite answer to the question of the comparative effectiveness of these two agents. This study thereby identified an important issue that both physicians interpreting comparative effectiveness studies and investigators from other registers and observational studies should be aware of.

The third study on comparative effectiveness in this thesis explored the possibilities of comparing the results of the RCTs performed with biologic agents in JIA (chapter 3.3). Although no differences in efficacy were found, the differences between the trials and the included study populations were significant, making the conclusions on comparative efficacy less reliable.

Biomarkers and monitoring tools

Unfortunately, the attempts to compare several treatments have not yet been conclusive on the question of comparative effectiveness of the available biologic treatments, especially when the biologic agents target the same cytokine. For an informed treatment decision

however, we would not only like to know what the differences in effectiveness are, but we would also like to have more insight into the effectiveness of a drug for specific patients. Ideally, there would be a distinctive feature of the patient or a test or biomarker we could perform that would perfectly guide treatment decisions.

In this thesis, the biomarker MRP8/14 was tested for its accuracy in the prediction of treatment response to TNF-inhibitors in non-systemic JIA and also for its accuracy in predicting a flare after withdrawal of etanercept treatment when remission was achieved (chapter 4.4). MRP8/14 serum levels proved to be associated with response to treatment with TNF-inhibitors and with relapse after discontinuation of etanercept. It seems to be wise to postpone etanercept discontinuation when MRP8/14 levels are high. These associations were present for both an experimental ELISA as well as a commercial ELISA, although the prognostic accuracy differed slightly (chapter 4.4). The availability of reliable commercial ELISA kits, plus the fact that MRP8/14 is a very stable protein even when serum is stored at room temperature, make it a suitable biomarker for clinical practice. On the other hand, the prediction of both events was not perfect, MRP8/14 serum levels explained only a small part of the variance in outcome when added to predictive clinical factors and MRP8/14 serum levels have up till now only been tested for MTX and etanercept treatment. Other predictors/biomarkers need to be identified to improve the recognition of patients who will benefit from the start of selected treatments and patients who can safely stop this treatment again.

Additionally, in an exploring investigation, anti-CarP antibodies were detected in serum samples of JIA patients and also found in ACPA and IgM-RF-negative patients (chapter 4.5). The diagnostic and prognostic value of these proteins still needs to be determined. This thesis also explored new options for monitoring JIA.

Bone mineral density evaluation of patients with JIA is part of an ongoing debate. Some physicians feel it should be closely monitored and treatment should be given based on this monitoring. Others are aware of the risk of low bone density, but feel monitoring is not necessary and the focus should be on prevention of decreased bone density by treating all high risk patients.[274] Both approaches are defendable, especially in the light of the difficulties in the determination of bone mineral density. DXA is the most used method for evaluation of bone mineral density, however it is not the gold standard.[201 240] That term is reserved for pQCT, which is unfortunately more expensive, less accessible and has a relatively high radiation exposure. The BoneXpert method for automated determination of bone age and bone mineral density based on hand radiographs proved feasible in JIA patients. It is very easy to use, relatively cheap, uses existing hand radiographs and is less

burdensome for the patient than the other methods. The bone mineral density measure derived from the BoneXpert however did not correlate well to the often used DXA method (chapter 4.2 and chapter 4.3). We therefore feel a comparison with the gold standard (pQCT) for bone mineral density evaluation is warranted if we want to determine the value of BoneXpert in the evaluation of bone mineral density in JIA patients. Caution is necessary when using the BoneXpert method for the determination of bone mineral density in this patient group, especially because the bone mineral density of the hand may be locally decreased.

We feel that training of patients in recognizing joints with arthritis should be further investigated to get patients to be more involved in their disease but also in the decision making process. Implementing a patient-reported joint count without training is not useful, as a patient reported joint-count had limited agreement with a joint-count performed by the treating physician (chapter 4.1). However, when patients report no active arthritis, the physician mostly agrees with them. These results were consistent with other studies investigating patient-reported joint counts in JIA and RA.[179-181] Furthermore we should determine what purpose we want a patient-reported joint count to serve. Instead of monitoring arthritis, we could also use it as a measure for the patient's wellbeing/pain due to the disease activity.

To conclude, we can say that etanercept is now very well studied and that it is effective and has a favourable safety profile, also in the very long term. Unfortunately, we have not been able to answer the question whether there is a difference in effectiveness between the available TNF-inhibitors. Furthermore, no single feature or biomarker is yet available to perfectly predict response to TNF-inhibitors. Other biomarkers and monitoring tools are still under investigation. For clinical practice it is therefore essential that the treating physician fully realizes why he or she prescribes a certain treatment. Additionally, participation in observational research will be vital in answering the questions we still have, as clinical trials will most likely be unable to provide those answers.

METHODOLOGICAL CONSIDERATIONS IN THE CURRENT AND FUTURE STUDIES

The ABC register

The ABC register was designed with the aim of studying the effectiveness and safety of etanercept (and later every biologic treatment) prescribed to children with JIA.[32] It was a national study in which every centre in which JIA patients were treated with biologic agents was included. It was one of the first registers studying biologic treatment, and

as such, contributed significantly to the literature on etanercept for JIA patients.[24 26-32 83 165 275-277] Because every participating centre had a representative in the ABC working group, everyone involved stayed up-to-date on developments in the register. Since the Netherlands is a relatively small country and lines between the investigators and participating physicians were short, we could ensure a dataset of high quality. Especially at the start of the ABC register, biologic treatment was new and everyone involved was very committed to the data collection. For reimbursement of biologic treatment, patients were required to be assessed on the same disease activity variables and the same time points as in the ABC register. A key strength of the register is therefore its very detailed prospective data collection, particularly in the first years of the study. Over the years, more and more patients were treated with biologic agents and biologic treatment became a normal part of clinical practice. Because data collection was at that point more time consuming and the participating physicians were less focused on the novelty and the importance of the data collection, the amount of missing data increased slightly. In the data analyses missing data was handled with multiple imputation methods where possible. The variables that were most often missing were the variables that were not routinely collected in all centres, such as the CHAQ and the accompanying VAS'.

While in the earlier years of the register we can be fairly certain to have included every JIA patient in the Netherlands starting biologic treatment, in later years it is possible that a few have been missed, for instance because less specialized clinics decided to treat the patient without consulting one of the participating centres. Patients enrolled in clinical trials had to be excluded because of competing interests. Still, because the large majority of JIA patients is treated by a specialized paediatric rheumatologists in one of the participating centres, we feel patient inclusion remained at a high and representative level.

No comparator group was included in the ABC register and its starting point was the prescription of a biologic agent. This limits the generalizability and the interpretation of the findings on effectiveness and safety of biologic agents. Because the ABC register follows daily clinical practice and therefore the prescription patterns adopted by the treating physicians, it is difficult to design an observational drug study with an appropriate comparator. There are several examples of studies in RA and JIA in which a comparator group is included.[153 278-281] Often these comparator cohorts consist of biologic-naïve patients with similar disease characteristics starting MTX treatment. Several statistical techniques are applied to correct for confounding in comparing the two groups. For this to be successful, all possible confounders have to be registered and there has to be some overlap between the groups that are compared.

The advantage of these studies is the possibility of comparing effectiveness and safety to comparable patients. This can be especially useful in comparing safety issues, as JIA itself may be associated with a change in risk for certain adverse events. By comparing two comparable groups treated in a different way, one can control for these background risks. As long as the groups are similar, at least to some extent, with regard to confounding factors, also the comparative effectiveness can be studied, thereby controlling for the natural course of the disease.
The disadvantage of the inclusion of a comparator group is the presence of unmeasured confounders, which is unavoidable. Additionally, especially in JIA patients who are almost all treated according to the same step-up regimen, finding overlap between the study population and the comparator group will most probably be problematic.
Subgroups could be studied separately, making use of the data of the ABC register. The small sample size in these studies limits the power of the analyses, and therefore the inferences that can be made based on the data.
Most of the data in the studies resulting from the ABC register are prospectively collected, which is one of the strengths of the register. However, for some analyses such as the long term follow-up study, part of the information was retrospectively retrieved from the treating physician. This limits the reliability of these data.

The observational study design

The observational study design itself has several strengths and weaknesses. In contrast to an RCT which is designed to evaluate short-term efficacy and safety in a standardized setting, the observational design is used to observe and apprehend the real-life use of biologic treatment and to capture its long term safety. Its biggest flaw is the lack of randomization. This gives rise to its greatest concern: confounding by indication. An observational drug study is always subject to the current treatment paradigm and every treatment decision is made by the treating physician. This means that some variables may be related to both the reason of prescription of a drug and to the outcome under study. Because subjects are randomized in an RCT, any differences between two groups that are compared are pure chance. Therefore, the effects measured are almost certainly the result of the intervention studied. In a study where confounding by indication is present and not corrected for, a claim on causality is very hard to prove.
Confounding by indication almost certainly plays a role in several analyses in this thesis. In trends analysis, but also in drug persistence analysis in switching biologic treatments, the changing treatment availability of the drugs studied most definitely influences the

analyses. The attitude of physicians towards biologic treatment changed together with the treatment availability. They timed biologic treatment earlier, and the patient characteristics of patients treated with biologic agents changed. Additionally, patients included in the start of the register had been waiting for a treatment option like biologic treatment for a long time, as their disease was refractory to other drugs. These are the changes we know of and we can try to correct for in analyses. It is however not unthinkable that unmeasured factors changed as well. This unmeasured confounding is a challenge for observational studies. Differences between two patient groups treated with different biologic agents were detected in two studies in this thesis. Attempts to adjust for these differences partly failed, thereby identifying an important issue for future observational studies into the comparative effectiveness and safety of biologic agents.

Drug studies in paediatric rheumatology

JIA is an uncommon disease that results in a small population available for drug studies. Moreover, biologic treatment is only prescribed to a subset of JIA patients, which limits the sample size of biologic drug studies even further. The increasing number of biologic agents available restricts the power of single drug studies in the small patient population in which they can be tested. Furthermore, the heterogeneity of the disease makes it even less possible to generalize the effectiveness of a drug to a particular patient. These limitations of drug studies in paediatric rheumatology cannot be influenced by investigators and have to be recognized and dealt with in the best possible way.

However, the design of studies and the outcome measures used can be influenced by researchers and regulators. In this thesis it was shown that two trial designs are often used in paediatric rheumatology: the classic RCT and the withdrawal trial. The outcome measure of the withdrawal trial is not the true efficacy of the drug, but the efficacy of the drug to suppress a flare. Particularly now that the patients who are treated with biologic agents are changing, the question rises whether the withdrawal design is really the most appropriate trial design. In future trials, less severely affected patients will be included, in whom a flare may be less likely, also when the drug is withdrawn. Additionally, patients will be continuing MTX treatment or other co-medication during trials, which may also suppress a flare when the experimental treatment is stopped. These changes will make it difficult to reach the primary endpoint in a withdrawal trial.

In paediatric rheumatology, and also in this thesis, numerous outcome measures are being used to evaluate drug effectiveness. These different outcome measures are contributing to less comparable results between studies. Additionally, now that the aim of treatment

has shifted to complete silencing of the disease, we should reconsider the definition of treatment efficacy. The ACRpedi response measures are most often used in RCTs and were also used to evaluate treatment response in this thesis.[44] In clinical trials, a patient who achieved an ACRpedi30 score is considered as responsive to treatment. In these times of changing treatment possibilities we will have to rethink our response measures. Do we accept an ACRpedi30 as an indication of effect of treatment, or should we aim higher? In addition, the patient population in which we consider biologic treatment is constantly changing, and now also includes patients with a lower number of joints involved. For these patients a proportional response measure may not capture the true response to treatment. In the cases series studying patients with persistent oligoarticular disease we therefore evaluated the separate disease activity variables to study effectiveness of etanercept.
The continuous disease activity score JADAS-10 was also used to evaluate disease activity in this thesis.[23] It is a composite sum score including four of the JIA disease activity variables, including ESR. It is a relatively new measure that is still being improved. Although definitions of high and minimal disease activity are now available, at the time of writing, no generally accepted definition of improvement on this continuous score was available, limiting the interpretation of a change in JADAS-10.[282-285] It is however a measure that because of its continuous nature is more appropriate to use in longitudinal analyses, and internationally used cut-offs will surely be available soon.
Drug persistence is a common way to evaluate effectiveness in observational studies. Being only a proxy for the true effectiveness, it can be influenced by several factors and is therefore less reliable as an effectiveness measure. As only etanercept was available for the treatment of JIA for a long time, the drug persistence for etanercept as first biologic treatment is likely to be influenced by the absence of other treatment options. Perhaps treatment with etanercept would have been stopped earlier had other possibilities been available. This may have resulted in an overestimation of the effect of etanercept. The same is true for the second course of biologic treatment.

SETTING THE AGENDA FOR FUTURE RESEARCH ON TREATMENT IN PAEDIATRIC RHEUMATOLOGY

The increasing treatment options for JIA have resulted in a shift in the aims of JIA treatment from managing the disease to achieving inactive disease and preventing long term damage. Although this aim is achieved in a large part of patients, still some patients with JIA cannot successfully be treated.

At this point, all available biologic agents are able to attenuate the signs and symptoms of the disease to some extent. The key, however, is to find the right treatment for an individual patient sufficiently early in the disease, so that damage can be prevented and the disease course can – possibly – be truly attenuated. To really go forward, advances are needed in several areas. Basic, translational and clinical research should work together to achieve these advances. Firstly, we need to improve our understanding of disease pathogenesis, so that we can better predict the disease course. Additionally, we need to improve our understanding of the working mechanism of medical therapies for JIA, both existing and new treatments. In that way we can better predict response to treatment and understand the chronicity of the disease in some patients, despite treatment. Finally, we need to combine basic research into pathogenesis and into targeting the inflammatory pathway with clinical research studying the comparative effectiveness and safety of the increasing therapeutic arsenal.

Pathogenesis, disease course and response to treatment

The development of new treatments goes hand in hand with an increasing understanding of the disease. Since the first development of TNF-inhibitors, these drugs and their effects have been extensively studied and other cytokines were targeted. This led to a shift in the perception of the inflammatory and immune response from a hierarchical and static pathway to an interconnected and dynamic network [286 287] Although we understand more of the cytokines involved, we cannot directly relate these to the disease course in an individual patient. To provide tailored treatment we need predictive factors that can truly predict the course of the disease and the response to treatment, starting with the classification of patients at diagnosis. The current diagnostic criteria formulated by ILAR are consensus based and classify JIA patients into different categories based on the number of joints involved, the antibody status and accompanying extra-articular symptoms.[1] Although the subdivision of JIA into these categories has resulted in a widely accepted and internationally applied classification, significant patient heterogeneity still remains with regard to the course and outcome of the disease.[288]

Future analyses should focus on combining the increasing knowledge on genotypes, gene expression, protein expression, and cellular phenotypes and the knowledge we have acquired over the years on predictive clinical features. An example of this combination is an analysis performed in the REsearch in Arthritis in Canadian Children, Emphasizing OUTcomes (REACHOut) and Biologically Based Outcome Predictors in JIA (BBOP) consortia, in which machine learning methods developed for pattern recognition were

applied to a defined set of demographic, clinical, laboratory, and cytokine expression data.[289] From this dataset, five patient clusters were identified, which were more clinically and biologically homogeneous than the ILAR categories and strongly predicted the disease course. Discriminating factors were the levels of circulating cytokines, profiles of cytokines specific to a certain immune response and established clinical variables (including ANA, which has also in other studies been suggested as a distinguishing feature). This is one of the first studies to apply new methodological techniques to a large database of new onset JIA patients to try and develop a new classification system, and hopefully more are to follow.

In addition to predicting the natural course of the disease attention should also be given to the possible modulation of the immune response. In RA the concept of a window of opportunity is becoming more and more established. Both in basic research as well as in treatment-strategy trials, this window of opportunity should be investigated, and the investigation of a switch from a step-up approach of treatment to a hit-hard, step-down approach can be considered.[77 78 286] Mirroring treatment strategies in RA, both combinations of a DMARD and a biologic agent and combination therapy consisting of multiple DMARDs could be subject of future investigations in JIA. A combination of approaches could work additively (or the addition of an extra treatment could be redundant), but a synergistic effect could also be possible.

The future of comparative effectiveness and safety

In the fast changing landscape of biologic treatment, comparative studies are necessary to investigate the effectiveness and safety of the different drugs. The JIA study population is too small to do this in RCTs, especially if there is a need to detect marginal differences in effects, as is the case if we want to base our choices of personalized treatment upon the evidence derived from such trials. Indirect comparisons or meta-analyses are possible only if RCTs are made more uniform. Another way of addressing the question of comparative is in an observational study. It is important that in the analyses of such observational studies, an appropriate adjustment is made for the confounding discussed earlier, whether biologic treatment is compared with biologic treatment or a non-biologic comparator.

National registers such as the ABC register have contributed hugely to the observational literature on biologic treatment, particularly on etanercept. However due to the rarity of JIA and the increasing biologic treatment options other than etanercept, no individual national study on biologic treatment will be able to answer questions on the effectiveness of less commonly prescribed biologics or rare adverse events. To answer these questions, a large

sample size is required. International efforts have therefore been made to combine data on biologics use from several countries across Europe.[290]

For several reasons, this thesis is the last that will result from the ABC register. Dutch data on biologic use are now recorded in a European database. The question remains whether a national database like the ABC register could still be of value. The use of biologic therapies differs a great deal across Europe, because of differences in availability and reimbursement. Additionally, general management strategies for JIA vary between countries. These differences have been shown in RA, but there is no reason to belief these do not exist in JIA.[291] There are population differences in the observed benefits of a treatment, but also in the observed number of adverse events, either because the local incidence rates are different, or because the quality of the data collection differs between countries. A national study on biologic treatment is very useful in informing treating physicians and national health policy on the prescribing behaviour and the resulting effects. The results of a national study can thereby assist in improving local practice. On the other hand, for a national register to fulfil such a role, it has to be embedded in a national health structure that makes use of all the data coming out of the register. To solely have a register to collect data is not useful, as the data collection and analysis should have direct implications for health policies. One could question if these prerequisites are present in the Netherlands, where no authority demands the collection of national data, and where only a very small number of patients will be treated with all different kinds of biologic agents. In addition, to truly inform national health policies it may also be more useful to have a different starting point for a register. Instead of the use of biologic agents, this could be the diagnosis of JIA. In that way we would be able to study all different treatments presently used for the treatment of JIA.

For combined analyses from different countries to be successful, consideration must be given to various factors. Information on the generalizability of the national data, the way patients are enrolled and the national regulations on the prescription of biologic agents all need to be collected. Data collection and outcome assessment must be uniform. Methodologies used should take into account the differences between countries. Sometimes this may lead to the conclusion that data across studies simply cannot be pooled. To make data from separate studies in RA as uniform as possible, an initiative has been started for combining data from drug studies[292 293]. It would be wise to undertake a similar action for studying drugs in observational studies in JIA. Although the use of large international databases is increasingly common (not in the least because of requirements of FDA and EMA), one should keep questioning whether the research questions of interest are still valid and whether they can be answered using pooled or combined data.

To conclude, classification at diagnosis, the use of biomarkers (including imaging) to predict response to therapy and true inactive disease, the timing and kind of therapy used, the use of combination or monotherapy and the clinical safety and effectiveness of different treatments should all be studied further. Putting all these pieces of the puzzle together could result in a tailored treatment approach by which we might be able to not only attenuate disease activity but also the disease course. All these different pieces of information could then help us re-evaluate and adapt treatment in every stage of the disease course to the current status of the patient.

Chapter 6. **Summaries**

ENGLISH SUMMARY

The main aim of this thesis was the evaluation of advances in the management of JIA. It focused on developments in the biologic treatment of JIA, using data from the ABC register. Additionally, it explored new biomarkers and methods for monitoring the disease activity, bone age and bone health of patients with JIA.

Chapter 2 started where the previous theses resulting from the ABC register left off: with the effectiveness of the first available TNF-inhibitors.

In **chapter 2.1** the effectiveness of TNF-inhibitors was evaluated for oligoarticular persistent JIA, an indication for which TNF-inhibitors are prescribed off-label. A total of 16 patients with this JIA category were included in the ABC register, most of them treated with etanercept. The majority of these patients had previously been treated with intra-articular steroid injections and MTX. Compared to other non-systemic patients included in the ABC register, more patients were tested positive for ANA and more patients had (a history of) uveitis. Treatment with a TNF-inhibitor decreased disease activity on all variables and more than half of patients achieved inactive disease within three months. Anti-TNF treatment therefore seems to be a justifiable option, when treatment with MTX and intra-articular steroid injections has failed.

For **chapter 2.2** patients from a previous sub-analysis from the ABC register were re-contacted. The previous analyses had evaluated HRQoL and functional outcome of these patients. The aim of this new study was to assess these subjects again, more than five years after etanercept was started. 43 of the originally included 53 patients participated. The HRQoL improvement shown after start of etanercept was sustained after a median of 8.5 years. Disease activity and disability scores were generally low. On daily life aspects, such as education and employment, patients functioned comparably or better than their peers. Persistence and possible deterioration of radiologic damage stress the importance of early treatment. Patients reported higher pain levels than at their last follow-up in the previous analysis, indicating that perceived pain needs attention, even when the disease is inactive.

The expanding biologic treatment options were investigated in **chapter 3**.

In **chapter 3.1** the trends in prescription behaviour observed in the ABC register over the period 1999-2012 were evaluated. An increasing number of patients were treated with an increasing diversity of biologic agents. Over the years, the patient profile changed, the decision to treat with biologic agents was taken earlier in the disease course and for patients with lower disease activity and who were diagnosed with other JIA categories.

Together with these changes, disease outcomes improved. Because so many factors changed over the observation period, it is hard to say whether these better outcomes can be attributed only to a more effective biologic treatment strategy. During the course of the study, new biologic agents became available and incorporated in treatment algorithms. For systemic JIA, anakinra became the biologic agent of choice. Although adalimumab was available for 4 years of the observation period, etanercept remained first choice for non-systemic patients.

The motivations of the paediatric rheumatologist to choose either etanercept or adalimumab for non-systemic JIA patients were evaluated in **chapter 3.2**. The presence of (a history of) uveitis was the most important factor directing the choice towards adalimumab. Factors specific for the paediatric population—such as painful adalimumab injections—as well as the physician's familiarity with the drug accounted for the preference for etanercept.

In **chapter 3.3** the comparative efficacy of the available biologic agents was the subject of interest. Because RCTs comparing biologic agents directly are lacking, an attempt was made to indirectly compare the results from the placebo-controlled trials in the literature. For this analysis, several trials had to be excluded, because there was a wide variation in trial design (withdrawal design vs. classical RCT) and patient characteristics (for example the disease duration and the JIA categories of the patients who were included). For both systemic and non-systemic JIA, three trials were found to be sufficiently comparable to include them in two comparison-networks. The short-term efficacy seemed similar across biologic agents (etanercept, adalimumab and abatacept) for polyarticular course JIA. For systemic JIA, anakinra, canakinumab, tocilizumab were found equally efficacious. As much dissimilarity remained, uniformity in trial design is hardly needed to be able to perform indirect comparisons in the future. For now, the paediatric rheumatologist has to rely on these indirect comparisons supplemented by observational data derived from cohort studies and safety, practical and financial arguments.

Chapter 3.4 is one of these examples for an observational study evaluating effectiveness of several biologic agents. It deals with the effectiveness of a second biologic agent after failure of etanercept, measured as drug persistence. Around 20% of patients treated with etanercept switched to a second biologic agent. For patients with non-systemic JIA, adalimumab and infliximab (both TNF-inhibitors) were equally effective. For patients with systemic JIA switching from etanercept to a second agent, anakinra was superior to a second TNF-inhibitor. Overall, effectiveness of the second biologic agent was lower than that of the first, and seemed especially low when the first biologic agent was discontinued

because of primary ineffectiveness. Switching does seem to be safe, and since limited treatment options are available for these patients, justifiable after etanercept failure.
In **chapter 3.5** an attempt was made to compare the effectiveness of the first biologic agent, focusing on the comparison of the two TNF-inhibitors approved for non-systemic JIA: etanercept and adalimumab. In this chapter, three ways of analysis were applied to the same dataset. A linear regression was fitted for the change in JADAS-10, with treatment as one of the covariates. A cox regression was fitted, also using treatment as a covariate, again using drug persistence as a proxy for treatment effectiveness. Thirdly, an attempt was made to construct a propensity score for the allocation of treatment, and to apply this propensity score in a logistic regression method with minimal disease activity as outcome measure. In the first two methods, no significant differences were found in effectiveness of the two TNF-inhibitors. The third analysis could not be brought to a successful end, because of the lack of overlap in patient characteristics between the two treatment groups, which may have been expected, based on chapter 3.2. This lack of overlap in confounding factors was the most important finding in this chapter. Physicians interpreting comparative effectiveness and safety studies, but also investigators from other registers and observational studies should be aware of this problem.
In **chapter 4** new monitoring tools for JIA were explored.
To investigate whether the patient is able to give information on the number of active joints with arthritis, and whether this information corresponds to the assessment of the treating physician, a patient-reported joint count was evaluated in **chapter 4.1**. At the outpatient clinic of the Erasmus MC, 75 JIA patients aged 12-21 were asked to mark joints with active arthritis on a mannequin before two subsequent clinic visits. The physician then performed a joint count without having seen the patient's assessment. In general patients had a low number of active joints (median 1 joint, indicated by the physician). Although the agreement on both the overall number of joints and on individual joints was moderate at the first clinic visit, it decreased at the second clinic visit. The sensitivity to change was only moderate for worsening patients. When a patient reported no arthritis, the physician agreed in almost all cases. However for active joints this agreement was lower as patients generally overestimated active arthritis. The reports on a patient-reported joint count may be more of a general indication of wellbeing for the patient. If we want to use it as a measure of arthritis in clinical practice, the possibility of training patients to recognize active disease should be investigated.
Since JIA patients are at risk for abnormal bone maturation and decreased bone mineral density. In **chapter 4.2** and **chapter 4.3** a new method to automatically determine both

in hand radiographs was studied. In **chapter 4.2** this new method, called BoneXpert, was found to be feasible and easy to use in 69 JIA patients included in the ABC register. To apply this method, radiographs have to be of reasonable quality and patients' bone age has to lie within the age ranges of the program. The patients in this study had delayed bone maturation and lower bone mineral density compared with healthy children. Subsequently, in **chapter 4.3** the estimates of bone mineral density derived from BoneXpert were compared with those derived from DXA. DXA, albeit not the gold standard for measuring bone mineral density in children, is the most frequently used method. The correlation between age and gender corrected scores from BoneXpert and DXA was low. The chapter concludes that for application of this new method in clinical practice, it has to be compared with the gold standard in measuring bone mineral density, which is (p)QCT.

In **chapter 4.4** the predictive value of MRP8/14 serum levels was investigated for the response to treatment in 88 non-systemic JIA patients starting TNF-inhibitors. Additionally the predictive value of this same marker was assessed for predicting a disease flare after the discontinuation of etanercept when remission on medication had been achieved. Both an experimental in-house ELISA and a commercially available ELISA kit were tested. A subgroup of JIA patients who responded well to anti-TNF treatment had high serum levels of MRP8/14. When remission was achieved and etanercept withdrawn, elevated MRP8/14 levels were associated with a higher chance to flare. On prediction of both events, the accuracy was not perfect. The two ELISAs tested performed equally.

Finally, in **chapter 4.5** serum samples from 234 patients included in three different cohorts were tested for the presence of anti-CarP antibodies, a novel antibody that was found to be associated with worse disease outcome in RA patients. Anti-CarP antibodies were more often present in the serum of JIA patients compared with healthy controls. Approximately half of the anti-CarP positive patients were also positive for anti-citrullinated antibody and/or IgM-RF. As this was an explorative analysis, the prognostic value of anti-CarP in JIA remains to be determined.

The last chapter of this thesis (**chapter 5**) comprises an overview of its findings, together with a discussion of the clinical implications and methodological considerations. It ends with a personal view of what the future of JIA research and drug studies in JIA should look like.

NEDERLANDSE SAMENVATTING

In dit proefschrift staan nieuwe ontwikkelingen in de behandeling van JIA centraal. Hierin worden twee aandachtsgebieden onderscheiden. Allereerst zijn gegevens van het ABC register gebruikt om de veranderde mogelijkheden in de behandeling met biologicals te bestuderen. Vervolgens zijn ook nieuwe biomarkers en methoden voor het monitoren van de ziekteactiviteit, de botleeftijd en de botgezondheid van JIA onderzocht.
Hoofdstuk 2 begint waar de onderzoekingen beschreven in eerdere proefschriften die voortkwamen uit het ABC register eindigden: bij de effectiviteit van de verschillende TNF-alfa blokkers voor de behandeling van JIA.
In **hoofdstuk 2.1** wordt onderzoek naar de werkzaamheid van TNF-alfa blokkers beschreven, wanneer deze medicijnen worden voorgeschreven aan patiënten met persisterende oligoarticulaire JIA. Deze diagnose is officieel geen indicatie voor behandeling met TNF-alfa blokkers. Toch werden in het ABC register 16 patiënten met deze JIA categorie geïncludeerd; 14 patiënten werden behandeld met etanercept en twee patiënten met adalimumab. Het grootste deel van deze patiënten werd eerder behandeld met MTX en intra-articulaire steroid injecties. Behalve dat ze minder aangedane gewrichten hadden dan de andere patiënten die in Nederland behandeld werden met biologicals, verschilden deze patiënten ook op andere eigenschappen van de overige patiënten. Zij testten vaker positief voor ANA en meer patiënten hadden (een voorgeschiedenis van) uveitis. Nadat behandeling met TNF-alfa blokkers was ingesteld daalde de ziekteactiviteit. Meer dan de helft van de patiënten had geen actieve artritis meer binnen drie maanden na start van de behandeling. De conclusie van dit hoofdstuk is dan ook dat behandeling van TNF-alfa blokkers een effectieve behandeling zijn voor patiënten met deze JIA categorie. De beslissing om deze patiënten te behandelen met TNF-alfa blokkers is te rechtvaardigen wanneer behandeling met MTX en intra-articulaire injecties niet effectief is gebleken.
Voor **hoofdstuk 2.2** werd met patiënten die eerder deel uitmaakten van een eerdere sub-analyse van het ABC register opnieuw contact opgenomen. Deze sub-analyse had laten zien dat de kwaliteit van leven gerelateerd aan de gezondheid (“health related quality of life” (HRQoL)) en het dagelijks functioneren van patiënten sterk vooruitgingen na de start van etanercept. Het doel van de nieuwe studie in hoofdstuk 2.2 is om HRQoL en het functioneren opnieuw te onderzoeken, meer dan vijf jaar na de start van etanercept. Van de oorspronkelijk 53 geïncludeerde patiënten namen 43 patiënten deel aan deze nieuwe studie. Zij gaven 8.5 jaar na het starten van etanercept aan een zelfde niveau van HRQoL te hebben als kort na de start. Een groot deel van de patiënten had geen artritis en voelde

zich weinig beperkt in het dagelijks leven. Opleidingsniveau en arbeidsparticipatie waren op hetzelfde niveau of zelfs hoger dan leeftijdsgenoten. Bij veel van deze patiënten was al een vorm van schade waarneembaar bij röntgenonderzoek bij de start van etanercept. Deze schade bleef aanwezig of was mogelijk soms zelfs verergerd op het moment van deze nieuwe studie. In onze ogen benadrukt dit de noodzaak van vroege behandeling. Opvallend is dat de patiënten meer pijn aangaven dan bij het laatste follow-up moment in de vorige studie. Pijn bij lage ziekteactiviteit is een grotendeels onbegrepen probleem, en verdient aandacht zowel in de spreekkamer als in verder wetenschappelijk onderzoek.

De toenemende behandelmogelijkheden met biologicals zijn onderzocht voor **hoofdstuk 3**. In **hoofdstuk 3.1** worden de trends in het gebruik van biologicals in het ABC register in de periode van 1999 tot 2012 beschreven. Een toenemend aantal patiënten werd in deze periode behandeld met biologicals en er werden meer verschillende middelen voorgeschreven. Het profiel van de patiënten die behandeld werden met biologicals veranderde over de jaren. Zo startten patiënten sneller na de diagnose JIA met behandeling met biologicals, bij een lager niveau van ziekteactiviteit. Naast patiënten met polyarticulaire en systemische JIA werden in latere jaren ook patiënten met de andere JIA categorieën behandeld met biologicals. Tijdens de studieperiode verbeterden ook de uitkomsten van patiënten die geïncludeerd werden. Omdat zoveel veranderingen tegelijk plaatsvonden kunnen deze verbeterde uitkomsten niet één op één verbonden worden aan de behandeling met biologicals.

De toename in biologicals betekende dat de kinderreumatoloog keuzes moest maken in de behandeling van de individuele patiënt. Voor patiënten met systemische JIA koos de kinderreumatoloog steeds vaker voor anakinra, zodat aan het einde van de studieperiode dit middel de eerste keus bleek voor deze JIA categorie. Ondanks dat adalimumab de laatste vier jaar officieel beschikbaar was voor non-systemische JIA bleef etanercept de meest voorgeschreven biological voor deze groep patiënten.

De keuze van de kinderreumatoloog voor ofwel etanercept ofwel adalimumab is het onderwerp van **hoofdstuk 3.2**. De behandelaars gaven aan dat de aanwezigheid van (een voorgeschiedenis van) uveitis de belangrijkste factor was om te kiezen voor adalimumab. Factoren die specifiek zijn voor de kinderreumatologische populatie (zoals de pijnlijke adalimumab injecties), samen met de bekendheid van etanercept bij de behandelend arts, zorgden voor een uiteindelijke voorkeur voor etanercept.

Vanaf **hoofdstuk 3.3** worden studies naar het verschil in effectiviteit tussen de verschillende biologicals beschreven. Omdat er geen gerandomiseerde trials zijn uitgevoerd die de werkzaamheid van de verschillende biologicals direct onderzoeken word in dit hoofdstuk

een poging gedaan om de beschikbare trials indirect te vergelijken. Een aantal trials kon niet geïncludeerd worden in deze indirecte vergelijking, omdat er grote variabiliteit was in de opzet van de verschillende studies ("withdrawal" vs. klassieke gerandomiseerde trial) en in de eigenschappen van de patiënten die geïncludeerd waren in de verschillende studies (zoals de ziekteduur en de JIA categorieën van deze patiënten). Twee vergelijkingsnetwerken konden worden geconstrueerd, een voor systemische en een voor non-systemische JIA. Beide netwerken bevatten drie trials die voldoende vergelijkbaar werden geacht voor deze analyse. De werkzaamheid van de verschillende biologicals op de korte termijn leek vergelijkbaar voor etanercept, adalimumab en abatacept bij de behandeling van non-systemische JIA. Voor de behandeling van systemische JIA leken canakinumab, anakinra en tocilizumab in gelijke mate werkzaam te zijn. Er waren echter nog steeds veel verschillen tussen de studies die in de indirecte vergelijking werden meegenomen. Voor het bepalen van de verschillen in werkzaamheid van deze middelen zijn trials die biologicals direct vergelijken hard nodig. Het is echter onwaarschijnlijk dat deze op korte termijn zullen worden uitgevoerd. Op dit moment moet de kinderreumatoloog afgaan op de indirecte vergelijkingen zoals de studie in dit hoofdstuk, gecombineerd met de resultaten van observationele studies, aangevuld met de eigen ervaring, praktische en financiële argumenten.

Hoofdstuk 3.4 is een voorbeeld van een dergelijke observationele studie. Hierin wordt de effectiviteit van verschillende biologicals vergeleken, wanneer deze voorgeschreven werden als tweede biological, nadat behandeling met etanercept niet voldoende effect bleek te hebben. Ongeveer 20% van de patiënten die behandeld werden met etanercept als eerste biological kregen een tweede biological voorgeschreven. Na onvoldoende respons op etanercept, bleken adalimumab en infliximab (beiden TNF-alfa blokkers) even effectief voor JIA patiënten non-systemische JIA. Voor patiënten met systemische JIA bleek anakinra beter werkzaam dan een tweede TNF-alfa blokker. De effectiviteit van een tweede biological was globaal genomen minder dan die van de eerste en leek vooral laag wanneer er primair geen respons was op de behandeling met het eerste biological. Het veranderen van biological lijkt wel veilig te zijn en, omdat maar weinig andere behandelmogelijkheden voorhanden zijn, te rechtvaardigen.

In **hoofdstuk 3.5** wordt het onderzoek naar de verschillen in werkzaamheid van de eerst-voorgeschreven biological besproken. In deze studie ligt de focus op de twee voor non-systemische JIA geïndiceerde TNF-alfa blokkers etanercept en adalimumab. Drie analysemethoden werden toegepast op dezelfde dataset. Als eerste werd een lineaire regressie toegepast, met als uitkomstmaat de verandering in JADAS-10. De behandeling

werd als covariaat meegenomen. Als tweede werd een Cox regressie uitgevoerd, opnieuw met de behandeling als covariaat, maar nu met de continuering van de behandeling als maat voor effectiviteit. Als laatste werd geprobeerd om een propensity score te construeren voor de toewijzing van behandeling met een bepaalde biological. Vervolgens zou deze propensity score in een logistisch regressiemodel worden meegenomen, met het bereiken van minimale ziekteactiviteit als uitkomstmaat. In de eerste twee methoden werden geen significante verschillen gevonden tussen werkzaamheid van de twee biologicals. De derde analyse kon niet volledig worden uitgevoerd, omdat er te weinig overlap was in de eigenschappen van patiënten die als confounders werden gezien. Dit was mogelijk te verwachten, gebaseerd op hoofdstuk 3.2. Het gebrek aan overlap in confounders is de belangrijkste bevinding in dit hoofdstuk. Artsen die onderzoek naar de verschillen in werkzaamheid van meerdere middelen interpreteren voor de klinische praktijk, maar ook onderzoekers van andere registers en observationele studies moeten zich bewust zijn van dit probleem.

In **hoofdstuk 4** liggen nieuwe biomarkers en methoden voor het monitoren van JIA onder de loep.

Hoofdstuk 4.1 beschrijft het onderzoek naar een door de patiënt gerapporteerde gewrichtsscore. Geprobeerd wordt de vraag te beantwoorden of de inschatting van de patiënt ten aanzien van het aantal gewrichten met actieve artritis overeenkomt met de beoordeling van de arts. Hiervoor werden op de jongerenpolikliniek van het Erasmus MC alle patiënten tijdens twee opeenvolgende polibezoeken gevraagd om actieve artritis aan te geven op een gewrichtspoppetje. De arts vulde vervolgens eenzelfde pop in, zonder die van de patiënt te hebben gezien. Over het geheel genomen werden weinig actieve gewrichten gescoord. De overeenkomst tussen arts en patiënt was redelijk tijdens het eerste invulmoment, echter deze was veel minder bij het tweede invulmoment. Als een patiënt aangaf dat er geen actieve artritis was, was de arts het hier bijna altijd mee eens. Wanneer de patiënt echter aangaf actieve artritis te hebben, was dit volgens de arts vaak een overschatting van de aanwezigheid van artritis. Mogelijk is de rapportage van de patiënt meer een reflectie van zijn algehele staat van welbevinden. Als we een dergelijke, door de patiënt ingevulde gewrichtspop voor de klinische praktijk willen gaan gebruiken, moeten we eerst onderzoeken of het mogelijk is de patiënt te trainen in het herkennen van actieve artritis.

JIA patiënten lopen risico een afwijkende bot-maturatie en verminderde botdichtheid te ontwikkelen. **Hoofdstuk 4.2** en **hoofdstuk 4.3** beschrijven de studies waarin een nieuwe methode om automatisch de botleeftijd en botdichtheid te bepalen (BoneXpert) wordt

geëvalueerd. Deze nieuwe methode meet de botleeftijd en botdichtheid gebaseerd op röntgenfoto's van de hand. Voor de studie in **hoofdstuk 4.2** werden handfoto's van 69 patiënten uit het ABC register onderzocht en geconcludeerd dat deze methode uitvoerbaar, snel en makkelijk bruikbaar is bij JIA patiënten. De handfoto's moeten wel van voldoende kwaliteit zijn en de botleeftijd van de patiënten moet binnen de grenzen van het programma liggen.

Voor de studie in **hoofdstuk 4.3** werd vervolgens de botdichtheidsbepaling van de BoneXpert vergeleken met die van de vaak gebruikte DXA scan. De scores, gecorrigeerd voor leeftijd en geslacht, correleerden minimaal. Aangezien DXA niet de gouden standaard is voor het bepalen van botdichtheid bij kinderen (dit is de pQCT), werd geconcludeerd dat BoneXpert met pQCT vergeleken zou moeten worden om zekerheid te verschaffen over de waarde van deze methode in de klinische praktijk van JIA.

In **hoofdstuk 4.4** wordt onderzoek naar de waarde van MRP8/14 in het serum van 88 non-systemische JIA patiënten voor het voorspellen van de respons op behandeling met TNF-alfa blokkers beschreven. Daarnaast is ook naar de waarde van deze marker gekeken voor het voorspellen van een opvlamming van de JIA wanneer etanercept gestaakt werd na het bereiken van remissie. De MRP8/14 bepaling werd gedaan met een door onderzoekers in Münster ontwikkelde ELISA en een commercieel verkrijgbare ELISA. Een hoog niveau van MRP8/14 in het serum bleek voorspellend voor zowel een goede respons op TNF-alfa blokkers als voor het opvlammen van de ziekte na het staken van etanercept, echter de bepaling had weinig toegevoegde waarde in een predictiemodel met andere klinische predictoren. Dit resultaat was hetzelfde voor beide bepalingsmethoden. De nauwkeurigheid voor het voorspellen van beide uitkomsten was echter niet perfect. MRP8/14 is een stabiele marker die reproduceerbaar met verschillende methoden bepaald kan worden. Mogelijk is er een toekomst voor deze marker in het monitoren van ziekteactiviteit in klinische trials. Voor de kliniek is de toegevoegde waarde op dit moment beperkt.

In **hoofdstuk 4.5** wordt een explorerende studie beschreven, die onderzoekt of anti-CarP antistoffen aanwezig zijn in het serum van JIA patiënten. Deze nieuwe antistof is bij RA patiënten geassocieerd met een slechtere prognose. Voor deze studie werd het serum van 234 JIA patiënten, afkomstig uit drie verschillende cohorten onderzocht. Anti-CarP antistoffen werden vaker aangetoond in het serum van JIA patiënten dan in het serum van gezonde controles. Ongeveer de helft van de anti-CarP positieve patiënten werden ook positief getest voor ACPA en RF antistoffen. Deze studie was een explorerende analyse, de prognostische waarde van anti-CarP moet nog nader worden bepaald.

Het laatste hoofdstuk van dit proefschrift (**hoofdstuk 5**) bevat een overzicht van alle

bevindingen van dit proefschrift. Deze bevindingen worden bediscussieerd in het licht van klinische implicaties en methodologische beperkingen. Het hoofdstuk eindigt met een blik op de toekomst van algemeen JIA onderzoek en onderzoek naar geneesmiddelen voor JIA.

Appendices

APPENDIX I – REFERENCES

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APPENDIX II – LIST OF ABBREVIATIONS

ABC	Arthritis and Biologicals in Children
ACPA	Anti-Citrullinated Protein Antibody
ACR	American College of Rheumatology
ACRpedi	ACR paediatric response score
Aba	Abatacept
ADA	Adalimumab
AE	Adverse Event
AIC	Akaike Information Criterion
Ana	Anakinra
ANA	Anti Nuclear Antibody
BA	Bone Age
BE	general Behaviour perceptions domain
BHI	Bone Health Index
BMAD	Bone Mineral Apparent Density
BMD	Bone Mineral Density
BMD_{LS}	BMD of the Lumbar Spine
BMD_{TB}	Total Body BMD
BMI	Body Mass Index
BP	Bodily Pain domain
CarP	Carbamylated Protein
CH	Change in Health domain
cBMD	cortical BMD
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Chilld Health Questionnaire
CI	Confidence Interval
CS	Corticosteroid
(s)DMARD	(synthetic) Disease Modifying Anti-Rheumatic Drug
DXA	Dual X-ray Absorptiometry
DXR	Digital X-ray Radiogrammetry
EMA	European Medicines Agency
ERA	Enthesitis Related Arthritis
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
FA	limitations on Family Activities domain
FC	Family Cohesion domain
FCS	Fetal Calf Serum
FDA	Food and Drug Administration
FU	Follow-up
GH	General Health perceptions domain
HAQ	Health Assessment Questionnaire
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HUI3	Health Utility Index Mark 3
IA	Intra-articular
IBD	Inflammatory Bowel Disease
ICC	Intra-Class Correlation
IL	Interleukin

ILAR	International League of Associations for Rheumatology
IM	Intramuscular
Infl	Infliximab
IQR	Interquartile Range
ISCED	International Standard Classification of Education
IV	Intravenous
JADAS	Juvenile Arthritis Disease Activity Score
JADI-E	Juvenile Arthritis Damage Index for Extra-articular damage
JAK	Janus Kinase
JC	Joint Count
JIA	Juvenile Idiopathic Arthritis
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
mAb	Monoclonal Antibody
MCS	Mental Component Summary score
MDA	Minimal Disease Activity
MH	Mental Health domain
MRP	Myeloid Related Protein
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
oJIA	Oligoarticular JIA
OR	Odds Ratio
PCS	Physical Component Summary score
PE	Emotional impact on the Parent domain
PF	Physical Functioning domain
PGA	Physician Global Assessment
pJIA	Polyarticular course JIA
pQCT	peripheral Quantitative Computed Tomography
psJIA	Psoriatic JIA
PT	impact on the Parent's personal Time domain
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RE	Role functioning: Emotional limitations domain
RF	Rheumatoid Factor
RP	Role functioning: Physical limitations domain
RR	Relative Risk
SAE	Serious Adverse Event
SE	Self Esteem domain
SF	Social Functioning domain
SF-36	Short Form 36
SI	Sacroiliac
sJIA	Systemic JIA
SRM	Standardized Response Mean
SSZ	Sulfasalazine
TM	Temporomandibular
TNF	Tumour Necrosis Factor
VAS	Visual Analogue Scale
VT	Vitality domain

APPENDIX III – CO-AUTHORS AND AFFILIATIONS

Co-authors from the ABC working group

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APPENDIX IV – DANKWOORD

Hier ligt het dan, het eindproduct van bijna vier jaar verdieping in de kinderreumatologie. In die vier jaar werd echter steeds duidelijker dat het niet alleen om dat eindproduct ging, maar even zoveel, of zelfs meer, om de weg daarnaartoe. Die weg leek soms onbegaanbaar, met zijwegen die tot niets leiden, en kronkelpaden waarvan de bestemming lang onduidelijk bleef, maar met beloning aan het eind. Bovenal was het echter een grote ontdekkingstocht met onderweg onverwachte ervaringen en ontmoetingen die leidden tot nieuwe inzichten, zowel op professioneel als persoonlijk vlak.

Voor zo'n tocht is een goede infrastructuur onontbeerlijk en gelukkig lag deze al voor mij klaar: de ABC-projecten liepen, opgezet door mijn gedreven voorgangsters. Door het hele land zorgden kinderreumatologen, fysiotherapeuten, reumaverpleegkundigen en doktersassistenten ervoor dat gegevens werden verzameld. Zonder hen waren mijn onderzoeken nooit van de grond gekomen.

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In de leescommissie en grote commissie nemen tot mijn groot plezier een aantal belangrijke wegwijzers plaats. Prof. dr. J.M.W. Hazes, beste Mieke, dank voor het warme bad dat de reumatologie de afgelopen twee jaar geweest is. Dear Kimme Hyrich, thank you for all your hospitality and advice, I hope we will keep in touch! Lieve Marinka, wat een eer om jou in mijn grote commissie te hebben, de cirkel is rond!

Beste Prof. dr. E.E.S. Nieuwenhuis, dank voor het plaatsnemen in de leescommissie en tot ziens in Utrecht! Beste Prof. dr. E.W. Steyerberg, dank voor het plaatsnemen in de leescommissie. Verder wil ik ook de overige leden van de grote commissie bedanken voor hun aanwezigheid.

Wat is er beter dan in goed gezelschap op reis gaan, met voldoende proviand. Gelukkig

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Liefste Will, de afgelopen twee jaar was je er altijd, ook al snapte je soms misschien weinig van al het ge-MD, MSc, PhD. Jij, zonnende zonnestraal, zorgde bij elk dipje dat ik direct weer op mijn knopjes was. Bij jou heb ik in ieder geval één bestemming gevonden. Thank you for being you!

APPENDIX V – LIST OF PUBLICATIONS

Janneke Anink, Koert M. Dolman, J. Merlijn van den Berg, Mira van Veenendaal, Taco W. Kuijpers, van Marion A.J. Rossum. Two-year outcome of juvenile idiopathic arthritis in current daily practice: what can we tell our patients? Clin Exp Rheumatol 2012;30(6):972-8.

Janneke Anink, Marieke H. Otten, Femke H.M. Prince, Esther P.A.H. Hoppenreijs, Nico M. Wulffraat, Joost F. Swart, Rebecca ten Cate, Marion A.J. van Rossum, J. Merlijn van den Berg, Koert M. Dolman, Yvonne Koopman-Keemink, Wineke Armbrust, Sylvia Kamphuis, Philomine A. van Pelt, Simone L. Gorter
Lisette W.A. van Suijlekom-Smit. Tumour necrosis factor-blocking agents in persistent oligoarticular juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children Register. Rheumatology (Oxford). 2013 Apr; 52(4):712-717

Marieke H. Otten, Femke H.M. Prince, **Janneke Anink**, Rebecca ten Cate, Esther P.A.H. Hoppenreijs, Wineke Armbrust, Yvonne Koopman-Keemink, Philomine A. van Pelt, Sylvia Kamphuis, Simone L. Gorter, Koert M. Dolman, Joost F. Swart, J. Merlijn van den Berg, Nico M. Wulffraat, Marion A.J. van Rossum, Lisette W.A. van Suijlekom-Smit. Effectiveness and safety of a second and third biological agent after failing etanercept in juvenile idiopathic arthritis: results from the Dutch National ABC Register. Ann Rheum Dis. 2013 May; 72(5):721-727.

Janneke Anink, Marieke H. Otten, Simone L. Gorter, Femke H.M. Prince, Marion A.J. van Rossum, J. Merlijn van den Berg, Philomine A. van Pelt, Sylvia Kamphuis, Danielle M.C. Brinkman, Wijnand A.A. Swen, Joost F. Swart, Nico M. Wulffraat, Koert M. Dolman, Yvonne Koopman-Keemink, Esther P.A.H. Hoppenreijs, Wineke Armbrust, Rebecca ten Cate, Lisette W.A. van Suijlekom-Smit. Treatment choices of paediatric rheumatologists for juvenile idiopathic arthritis: etanercept or adalimumab? Rheumatology (Oxford). 2013 Sep; 52(9):1674-1679.

Marieke H. Otten*, **Janneke Anink***, Sandra Spronk, Lisette W.A. van Suijlekom-Smit. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis. 2013 Nov; 72(11):1806-1812.
**Contributed equally*

Petra C. E. Hissink Muller*, **Janneke Anink***, Jing Shi*, E.W. Nivine Levarht, Tjitske H. Reinards, Marieke H. Otten, Maarten J.D. van Tol, Els C.M. Jol-van der Zijde, Danielle M.C. Brinkman, Cornelia F. Allaart, Esther P.A.H. Hoppenreijs, Yvonne Koopman-Keemink, Sylvia Kamphuis, Koert Dolman, J. Merlijn van den Berg, Marion A.J. van Rossum, Lisette W.A. van Suijlekom-Smit, Marco W. Schilham, Tom W.J. Huizinga, Rene E.M. Toes, Rebecca ten Cate, Leendert A. Trouw. Anticarbamylated protein (anti-CarP) antibodies are present in sera of juvenile idiopathic arthritis (JIA) patients. Ann Rheum Dis. 2013 Dec; 72(12):2053-2055.
**Contributed equally*

Marieke H. Otten*, **Janneke Anink***, Femke H.M. Prince, Marinka Twilt, S.J. Vastert, Rebecca ten Cate, Esther P.A.H. Hoppenreijs, Wineke Armbrust, Simone L. Gorter, Philomine A. van Pelt, Sylvia S.M. Kamphuis, Koert M. Dolman, Joost F. Swart, J. Merlijn van den Berg, Yvonne Koopman-Keemink, Marion A.J. van Rossum, Nico M. Wulffraat, Lisette W.A. van Suijlekom-Smit. Trends in prescription of biological agents and outcomes of juvenile idiopathic arthritis: results of the Dutch national Arthritis and Biologics in Children Register. Ann Rheum Dis. 2014 Mar 18.
**Contributed equally*

Janneke Anink*, Charlotte M. Nusman*, Lisette W.A. van Suijlekom-Smit, Rick R. van Rijn, Mario Maas, Marion A.J. van Rossum. Automated determination of bone age and bone mineral density in patients with juvenile idiopathic arthritis: a feasibility study. Arthritis research & therapy. 2014 Aug 27; 16(5):424.
**Contributed equally*

Maryanne E. Dijkstra*, **Janneke Anink***, Philomine A. van Pelt, Johanna M.W. Hazes, Lisette W.A. van Suijlekom-Smit. Patient-reported Joint Count in Juvenile Idiopathic Arthritis: The Reliability of a Manikin Format. J Rheumatol 2014.
**Contributed equally*

Janneke Anink, Femke H.M. Prince, Maryanne Dijkstra, Marieke H. Otten, Marinka Twilt, Rebecca ten Cate, Simone L. Gorter, Yvonne Koopman-Keemink, Marion A.J. van Rossum, Esther P.A. Hoppenreijs, Lisette W.A. van Suijlekom-Smit. Long-term quality of life and functional outcome of patients with juvenile idiopathic arthritis in the biologic era; a longitudinal follow-up study in the Dutch Arthritis and Biologicals in Children register. (submitted for publication)

Janneke Anink, Mark Lunt, Kimme L. Hyrich, Lisette W.A. van Suijlekom-Smit. Comparing effectiveness of biologic agents for JIA in an observational study design: the challenge of confounding by indication. (submitted for publication)

Charlotte M. Nusman*, **Janneke Anink***, Marieke H. Otten, Marion A.J. van Rossum, Rick R. van Rijn, Mario Maas, Lisette W.A. van Suijlekom-Smit. Bone health of patients with juvenile idiopathic arthritis: a comparison between DXA and digital radiogrammetry. (submitted for publication)
**Contributed equally*

Janneke Anink, Lisette W A Van Suijlekom-Smit, Marieke H Otten, Femke Prince, Marion A.J. van Rossum, Koert Dolman, Esther P.A.H. Hoppenreijs, Rebecca ten Cate, Simona Ursu, Lucy Wedderburn, Gerd Horneff, Michael Frosch, Thomas Vogl, Faekah Gohar, Dirk Foell, Johannes Roth, Dirk Holzinger. MRP8/14 serum levels as predictor of response to starting and stopping anti-TNF treatment in juvenile idiopathic arthritis. (submitted for publication)

APPENDIX VI – PHD PORTFOLIO: SUMMARY OF PHD TRAINING AND TEACHING

Erasmus MC Department: Paediatrics - Paediatric Rheumatology
Research School: Molecular Medicine (MolMed)
PhD period: February 2011 – February 2015
Promotor: Prof. Dr. A.J. van der Heijden
Co-promotor: Dr. L.W.A. van Suijlekom-Smit

1. PhD training	Year	Workload
General academic skills		
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1.0
Biomedical English Writing and Communication	2012	4.0
Course Research Integrity	2012	2.0
PhD Curriculum TULIPS	2014-2015	4.0
Research skills	2011-2013	40
Master of Science Clinical Epidemiology		
Core curriculum:		
Study Design	2012	4.3
Biostatistical Methods 1	2011	5.7
Clinical Epidemiology	2011	5.7
Methodological Topics in Epidemiologic Research	2012	1.4
Biostatistical Methods 2	2011	4.3
In-depth courses		
Courses for the Quantitative Researcher	2012	1.4
Missing Values in Clinical Research	2012	0.7
Quality of Life Measurements	2012	0.9
Repeated Measurements in Clinical Studies	2012	1.4
Advanced Topics in Decision Making	2012	1.9
Epidemiology of Infectious Diseases	2012	1.9
Summer programme		
Principles of Research in Medicine	2011	0.7
Clinical Decision Analysis	2011	0.7
Methods of Public Health Research	2011	0.7
Markers and Prognostic Research	2011	0.7
The practice of Epidemiological Analysis	2011	0.7
Pharmaco-epidemiology	2011	0.7
Topics in Meta-analysis	2012	0.7
Case-control studies	2012	0.7
History of Epidemiologic Ideas	2012	0.7
Logistic Regression	2012	1.4

Seminars and workshops		
PhD-day, Sophia Children's Hospital Rotterdam	2011-2014	1.2
Young Investigators Day, Paediatric Association of the Netherlands	2011-2014	1.2
Young Investigators Meeting of the Paediatric Rheumatology European Society (PReS)	2012-2014	0.9
Paediatric Rheumatology European Society (PReS) Research Course, Genova	2012	1.4
1st EULAR Registers and Observational Drug Studies (RODS) Meeting, Prague	2013	0.5
International Conferences		
Combined European Congress of Rheumatology (EULAR) and Paediatric Rheumatology (PReS) Berlin	2012	1.0
American College of Rheumatology Annual Meeting, Washington D.C. [poster presentation]	2012	1.0
European Congress of Rheumatology (EULAR), Madrid [oral presentation]	2013	2.0
Congress of the Paediatric Rheumatology European Society (PReS), Ljubljana [poster presentations]	2013	1.0
American College of Rheumatology Annual Meeting, San Diego [poster presentations]	2013	1.0
European Congress of Rheumatology (EULAR), Paris [poster presentation]	2014	1.0
Congress of the Paediatric Rheumatology European Society (PReS), Belgrade [poster presentations]	2014	1.0
2. Teaching		
Lecturing		
Working group on Diagnostic tests in the Epidemiology course for 4th year medical students	2014	1.0
Supervising Master's theses		
M. Dijkstra, medical student, Erasmus University	2013	3.0
M. Sarwar, medical student, Erasmus University	2014	3.0
Other		
Peer review of articles for international scientific journals	2012-2014	2.0

APPENDIX VII – ABOUT THE AUTHOR

Biography

Janneke has always been fascinated by how things work, whether it's languages, ideas or people. While she began her academic career enjoying extended philosophical debates, she quickly realized that she found empirical science far more compelling. However, she finds working with people too fulfilling to confine herself purely to laboratory work. Working with physically and mentally disabled children was a formative experience that confirmed her interest in the social and psychological side of biomedical sciences.

Janneke revels in the opportunity to investigate a subject in depth, which is why a research project appealed to her. She enjoyed discussing methodology during her PhD training and being able to contribute evidence that can be of use in clinical practice. Now her thesis is completed, she is looking forward to combining clinical work with science in a future career as a paediatrician, starting with a position in the paediatrics department at the WKZ, Utrecht in 2015.

Curriculum Vitae

Name	Janneke Anink
Titles	MD, MSc Clinical Epidemiology
Date of birth	30 March 1982
Place of birth	Amsterdam

Education

2013	TULIPS PhD Curriculum, Master classes in Paediatric Science
2011-2013	Master of Science Clinical Epidemiology, Netherlands Institute for Health Sciences (NIHES), Erasmus University Rotterdam
2010	Medical doctor degree, University of Amsterdam – Academic Medical Centre (AMC) Amsterdam, Cum laude (30 July 2010)
2010	Final internships: Department of Paediatrics AMC Amsterdam Department of Paediatrics, several hospitals, Dehradun, India
2007 – 2010	Medical Finals, University of Amsterdam – AMC Amsterdam
2003 – 2007	Master's degree medicine, University of Amsterdam - AMC Amsterdam
2002 – 2003	Biomedical Sciences, propedeuse/foundation year, University of Amsterdam

2001 – 2002	Linguistics, second year, University of Amsterdam
2000 – 2001	Philosophy, propedeuse/foundation year, University of Amsterdam
1995 – 2000	Secondary school, Gymnasium, Ecumenical Secondary School “Het Baken”, Almere

Clinical work

2010-2011	Paediatric resident, department of Paediatrics, Zaans Medical Centre, Zaandam (6 months), Tutor: DJ Blom, MD
2004 – 2010	Group leader/ personal coach Philadelphia Care, guidance and care for children and adolescents (3 to 25 years old) with a physical and/or mental development disorder and/or behavioural problems.

Research

2011-2015	PhD training, National study on Arthritis and Biologicals in Children (ABC-project), department of paediatrics and paediatric rheumatology, Sophia Children’s Hospital, Erasmus Medical Center, Rotterdam. Project leader L.W.A. van Suijlekom-Smit, MD, PhD Head of department Prof. A.J. van der Heijden, MD, PhD
2008-2011	Retrospective study of short term outcome of Juvenile Idiopathic Arthritis, treated following current treatment strategy, department of paediatrics and paediatric rheumatology Emma Children/s Hospital, Academic Medical Center Amsterdam Tutor: M.A.J. van Rossum, MD, PhD

STELLINGEN BEHOREND BIJ HET PROEFSCHRIFT

ADVANCES IN THE MANAGEMENT OF JUVENILE IDIOPATHIC ARTHRITIS

THE COMING OF AGE OF BIOLOGIC TREATMENT

De sterk verbeterde behandelingsresultaten sinds de introductie van biologicals maken het noodzakelijk als volgende stap de middelen onderling te vergelijken en de timing van de behandeling aan te scherpen om inactieve ziekte te bereiken voordat schade is ontstaan. *(Dit proefschrift)*

De verbetering van kwaliteit van leven, bereikt door behandeling met etanercept bij patiënten met eerder refractaire JIA, blijft op lange termijn behouden. *(Dit proefschrift)*

Chronische pijn blijkt ook als er geen actieve artritis is, de kwaliteit van leven van JIA patiënten te beïnvloeden, dit is een complex probleem wat opheldering behoeft. *(Dit proefschrift)*

De keuze tussen de diverse biologicals wordt noodzakelijkerwijs ingegeven door resultaten uit onderzoek met weinig bewijskracht en persoonlijke ervaring van de kinderreumatoloog; deze “confounding by indication” bemoeilijkt de onderlinge vergelijking van biologicals in observationele studies. *(Dit proefschrift)*

Alle instanties betrokken bij de ontwikkeling en goedkeuring van nieuwe middelen voor de behandeling van JIA moeten zorg dragen voor meer uniformiteit in uitkomstmaten en design van klinische trials; meta-analyses worden dan mogelijk en de beschikbare gegevens van de kleine onderzoekspopulatie worden zo optimaal gebruikt. *(Dit proefschrift)*

Parents and children seek, and deserve, the assurance that comes from using medications rigorously studied in children rather than relying on a leap of faith based on adult trials. *(DeWitt et al, 2008 Arthritis and Rheumatology)*

Authors have the duty to make all their research publicly available, the positive as well as the negative or inconclusive results. This duty should extend to editors and reviewers of scientific journals. *(Adapted from the declaration of Helsinki)*

By considering RCTs and observational study designs complimentary, it might be possible to address questions faster, cheaper, and perhaps even better than either approach alone. *(Merkow et al, 2013 JAMA)*

Real shared decision making involves finding out what matters to the patient, to what extent they want to be empowered, and introducing scientific evidence in a way that informs a dialogue about what best to do, how and why. *(Greenhalgh, 2014 BMJ)*

It is important to give every doctor an interest in educating the public scientifically. *(George Bernard Shaw, 1909)*

A little nonsense now and then is relished by the wisest men. *(Charlie and the Chocolate Factory, Roald Dahl, 1964)*