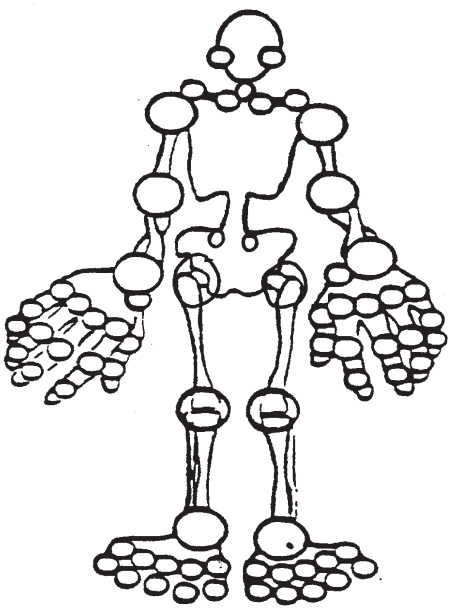
A decade of biologic treatment observation in juvenile idiopathic arthritis:
lessons learned from the Dutch ABC Register

Marieke H. Otten



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A Decade of Biologic Treatment Observation in Juvenile Idiopathic Arthritis

Lessons learned from the Dutch ABC register

Tien jaar behandeling van juveniele idiopathische artritis met biologicals

Wat hebben we geleerd van het Nederlandse ABC register

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.G. Schmidt

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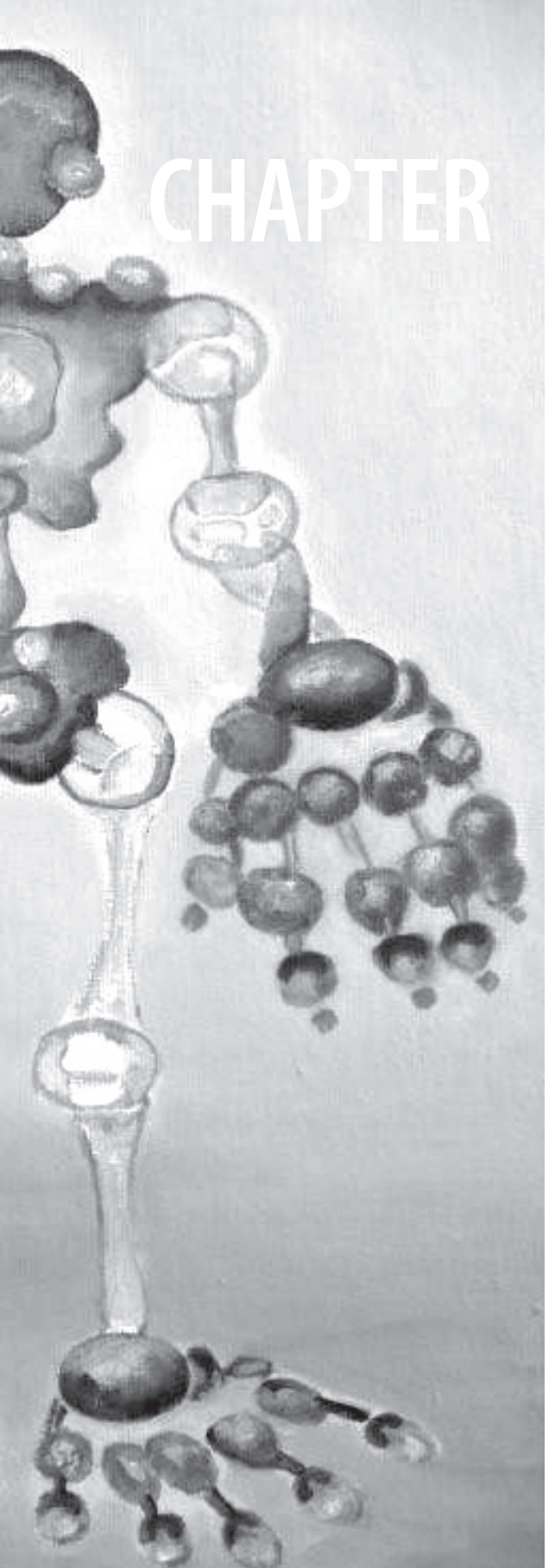

CHAPTER 1

Introduction to thesis

RATIONALE

Since 1999, the treatment of juvenile idiopathic arthritis (JIA) has been extended with a new category of drugs: biologic agents (also known as biologicals or biologic disease modifying anti-rheumatic drugs). Biologic agents consist of natural proteins, like antibodies and cytokines, and have been developed to target one or more steps of the immune response.[1] Elucidation of many of the cellular and molecular mechanisms of the immune system involved in inflammatory arthritis has resulted in an increasing development of different biologic agents and, in the future, this number will expand even further.

Tumour necrosis factor (TNF) is a proinflammatory cytokine that plays a central role in the pathogenesis of juvenile idiopathic arthritis.[2] In systemic disease, interleukin (IL)-1 (a proinflammatory cytokine synthesised by fibroblasts in the synovium and macrophages) and IL-6 (concentrations of which correlate with fever, disease activity, and platelet counts) are also thought to be important.[2-5] If inhibition of these cytokines is not sufficient, other drugs that aim at T cell blockade and B cell depletion are available.[6] Only etanercept (TNF-alpha receptor antagonist), adalimumab (anti-TNF-alpha antibody), abatacept (selective T-cell co-stimulation modulator) and tocilizumab (IL-6 receptor antibody) have been approved by the European Medicines Agency and the Food and Drug Administration for the treatment of JIA. Until now, also infliximab (anti-TNF-alpha antibody), anakinra (IL-1 receptor antagonist), canakinumab (anti-IL-1 antibody) and rilonacept (IL-1 receptor antagonist), though not approved, are available options or under investigation for the treatment of JIA.

All of the above mentioned agents have been studied in randomized controlled clinical trials with inclusion of JIA patients.[5, 7-12] But after approval and sometimes off-label use in daily clinical practice, prospective observational studies are crucial to evaluate the long-term effectiveness and safety in a non-selected patient group. Furthermore, additional information with regard to the optimal use and the use in specific subgroups of patients is required. These studies are known as Phase IV post-marketing surveillance studies. Because of the long-term aspect and the requirements of studying a large population, such studies have for practical and financial reasons an observational character, as for example the Dutch national Arthritis and Biologics in Children (ABC) Register.

STUDY DESIGN: THE DUTCH NATIONAL ABC REGISTER

The ABC Register is a multicenter prospective observational study that aims to include all JIA patients in the Netherlands who use or previously used biologic agents. It has been founded in 2003, includes prospectively collected data since 1999 and data collection is still ongoing. Patients enrolled in clinical trials are not included because of compet-

ing interests. The register was started with the introduction of etanercept and aimed to include all patients treated with TNF-alpha blockers, but in 2008 it was extended to the inclusion of all biologic agents besides TNF-alpha blockers. The Register became web-based in 2008 to facilitate its use for participating physicians and to guarantee accuracy and up-to-date data.[13] The study protocol was approved by the Medical Ethics Committee at Erasmus Medical Center Rotterdam and by all participating hospitals. The participating hospitals include all university hospitals in The Netherlands, specialized rheumatology clinics and other hospitals with a special interest in paediatric rheumatology. (Box. participating hospitals)

BOX 1. Participating hospitals ABC project

University hospitals
Academic Medical Center, Emma Children's Hospital, Amsterdam
University Medical Center, Beatrix Children's Hospital, Groningen
Leiden University Medical Center, Leiden
Maastricht University Medical Center, Maastricht
St. Radboud University Hospital, Nijmegen
Erasmus MC, Sophia Children's Hospital, Rotterdam
University Medical Center, Wilhelmina Children's Hospital, Utrecht

Specialized rheumatology clinics
Reade Institute, location Jan van Breemen, Amsterdam
St Maartenskliniek, Nijmegen

Other hospitals with a special interest in paediatric rheumatology
St. Lucas Andreas Hospital Amsterdam
Hagaziekenhuis Juliana Children's Hospital, The Hague

The patients' characteristics and disease history, such as gender, date of birth, date of JIA onset, JIA category, medical history and previous used medications before introduction of a biologic agent, are recorded at inclusion in the ABC Register.
Data-entry times are at start of each biologic agent, after 3 months of treatment, after 6 months (follow-up moment added in a later phase), after 15 months and yearly thereafter, until the patient is transferred to adult care. During these data-entry times, the use of biologic agents, use of concomitant medications and disease activity are recorded.

Evaluation of disease activity consists of the following set of variables:
1. Physicians' global assessment of disease activity on a visual analogue scale (VAS) (range 0-100 mm, 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 (VAS, range 0-100 mm, 0 best score)
4. Global assessment of wellbeing by patient/parent (VAS, range 0-100 mm, 0 best score)
5. Number of joints with arthritis
6. Number of joints with limited motion
7. Laboratory parameter for inflammation: erythrocyte sedimentation rate (ESR, mm/hour)

In addition to entering follow-up data at start, after 3, 6, 15 months and then yearly, extra data-entry times were at the time of any important events including, when biologics were discontinued, type of biologic switched or when there were safety concerns.

Furthermore, several add-on projects have been embedded within the ABC Register:

1. In a subset of centres, serum samples are collected at start of treatment, after 3 months, and yearly thereafter. Aim of the analyses is to better monitor and predict biologic treatment response. These analysis include antibodies against biologic agents and biomarkers.(Addendum)
2. Since 2003 a subset of patients included in the ABC Register receives X-rays of all affected joints yearly.
3. Between 2003 and 2010, patients from the Sophia Children's hospital in Rotterdam underwent a dual-energy X-ray absorptiometry (DXA) scan at start of etanercept treatment, after 15 months, and yearly thereafter to evaluate the bone mineral density.(Chapter 3.5)
4. Seven centres agreed to prospectively collect additional health-related quality of life questionnaires and cost-diaries from patients who started etanercept treatment from 2003 until 2006.[14-15]

Until 2012, over 400 JIA patients with more than 2,500 data-entry times have been included. The majority of patients (>95%) have been treated initially with etanercept, but adalimumab and anakinra are prescribed increasingly as first introduced biologic agent. Around 20% of patients switched to a second biologic agent. Total follow-up duration of all included patients has exceeded 1,000 patient-years.

OBJECTIVE AND OUTLINE OF THESIS

The main objective of the ABC register is to describe the prescription of biologic agents in daily clinical care and to evaluate the observed responses to biologic treatment (long-term effectiveness and safety) in a large JIA study population. Earlier publications from the ABC register focused on the use of etanercept and answered questions on the long-term effectiveness and safety, the quality of life among patients that initiated etanercept, the cost-effectiveness and the optimal dosing regimens of etanercept. In this thesis, studies were conducted to evaluate and compare the effectiveness of all biologic agents used in JIA and to gain further insight in the response and safety to etanercept treatment.

In **Chapter 2**, an overview of the literature is given. **Chapter 2.1** provides a general review on the diagnosis and management of juvenile idiopathic arthritis in where the place of biologic agents in current treatment strategies is evaluated. In detail, the conducted randomized controlled clinical trials on the different available biologic agents for JIA patients are critically appraised and, where possible, compared indirectly (**Chapter 2.2**). In **Chapter 3** the effectiveness and safety of first introduced biologic agents in previously biologically-naive Dutch JIA patients are presented. **Chapter 3.1** provides an overview of the effectiveness and safety of etanercept and evaluates factors associated with response to etanercept treatment, while **Chapter 3.2, 3.3, and 3.4** focus on the effectiveness of TNF-alpha blocking agents in the less prevalent JIA categories. In **Chapter 3.5** the long-term effects of etanercept on the patients' growth and bone status are given. **Chapter 4** demonstrates treatment strategies after failure of etanercept. This includes an evaluation of delayed clinical responses to etanercept (**Chapter 4.1**) and of switching to other biologic agents after failing etanercept (**Chapter 4.2**). Trends in prescription of biologic agents in JIA are reported in **Chapter 5**. **Chapter 5.1** describes the trends between 1999 and 2010 in prescription behaviour of physicians and subsequently the association with observed outcomes. **Chapter 5.2** focuses on the differences between patients that receive etanercept and adalimumab as first biologic. As an addendum, **Chapter 6** reports an international effort (Germany, England and The Netherlands) that evaluated whether the biomarker MRP8 and MRP14 protein complex indicates disease activity and predicts relapses in systemic JIA. **Chapter 7** provides a general discussion in which our epidemiological results of the Dutch population treated with biologic agents are compared to other studies and this chapter concludes with implications of future research. Finally, in **Chapter 8** a summary of this thesis is given.

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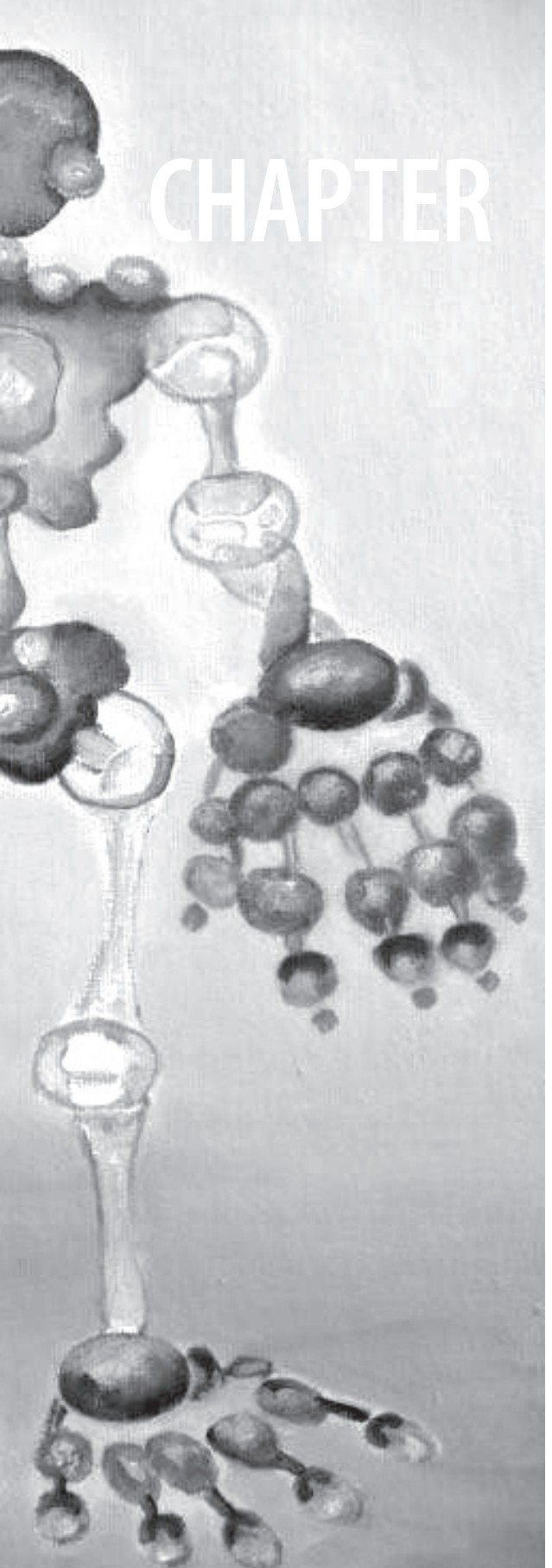
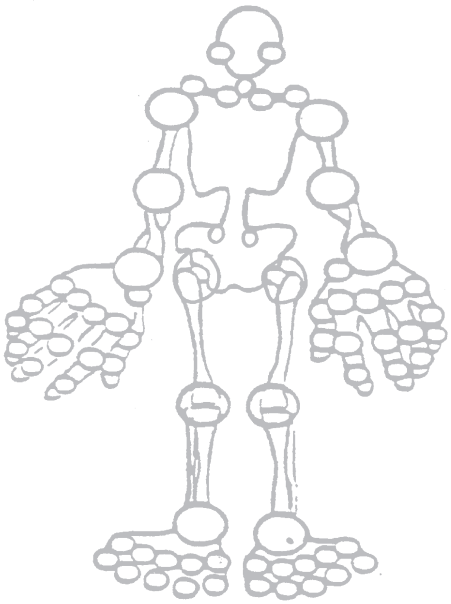


CHAPTER 2

Overview of the literature

CHAPTER 2.1

Diagnosis and management of JIA



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ABSTRACT

Juvenile idiopathic arthritis is the most common cause of chronic arthritis in childhood; a review of 34 epidemiological studies showed that 0.07-4.01 per 1000 children worldwide are affected.[w1] It is characterised by joint inflammation that often leads to joint destruction with physical disability and chronic pain that affects daily life.[1] During the past decade, increased understanding of the disease has improved treatment, particularly through earlier diagnosis and new treatments that help to prevent long term damage to joints. Earlier this year, the British Society for Paediatric and Adolescent Rheumatology published standards of care for children and young people with juvenile idiopathic arthritis, which outlined the importance of involving different disciplines within healthcare.[2] We review recent advances in the diagnosis and management of juvenile idiopathic arthritis, focusing on evidence from randomised controlled trials, cohort studies, systematic reviews, and current guideline.

SUMMARY POINTS

- § Early recognition and early aggressive treatment of juvenile idiopathic arthritis prevent joint damage and allow for normal development and growth.
- § The disease is heterogeneous and complex, so patients benefit from regular review and management by experts in a multidisciplinary team.
- § The disease currently has no cure, but clinical remission is a realistic treatment goal.
- § Biologic disease modifying anti-rheumatic drugs are a new and effective treatment for severe disease, but they increase the risk of infection; more data on long term adverse events need to be obtained from registries.
- § Trials need to determine the optimal treatment strategies with synthetic and biologic disease modifying anti-rheumatic drugs.

SOURCES AND SELECTION CRITERIA

As well as using our personal reference collections, we searched Medline, Embase, and Cochrane Central for clinical studies and reviews using the keywords "juvenile idiopathic arthritis", "juvenile rheumatoid arthritis", "juvenile chronic arthritis", "diagnosis", "treatment", "therapy", "non-steroidal anti-inflammatory drugs", "corticosteroids", "disease modifying anti-rheumatic drugs", "biologics", and "biologicals." We also reviewed guidelines from the British Society for Paediatric and Adolescent Rheumatology and the Royal Australian College of General Practitioners.

WHAT IS JUVENILE IDIOPATHIC ARTHRITIS AND WHO GETS IT?

Juvenile idiopathic arthritis (formerly juvenile chronic arthritis in Europe and juvenile rheumatoid arthritis in North America) covers a heterogeneous group of conditions more accurately described as subtypes (also known as categories).[w2-w4] The disease encompasses all forms of arthritis that begin before the age of 16 years, persist for more than six weeks, and are of unknown cause.[3] It is thought to be a multifactorial autoimmune disease with environmental and genetic contributory factors.[4] The heterogeneity of the subtypes and changes in terminology and classification make it difficult to interpret studies on the role of the environment.[5] The most common risk factors are infections in combination with genetic susceptibility. Many other factors, such as stress and maternal smoking, are thought to contribute to the pathogenesis. Juvenile idiopathic arthritis is a complex genetic disease with multiple genes involved. Individual cohort studies have confirmed and replicated several associations between juvenile idiopathic arthritis and variants in the histocompatibility (HLA) genes but the strength of the associations differ for each disease subtype.[w5] A large number of non-HLA candidate genes have been tested for associations, but only a few such as protein tyrosine phosphatase (PTPN22) and macrophage inhibitory factor (MIF) have been confirmed. A multiethnic Canadian cohort study showed a moderately increased risk for European origin compared with African, Asian, or Indian origin, and that subtypes differ significantly between ethnic groups (table 1).[6] The typical age of onset also depends on subtype.[w6] Table 1 lists the subtypes according to the currently accepted classification. Increased knowledge about the disease will probably refine the classification further. This might provide homogeneous subgroups for research and lead to tailored disease management.

TABLE 1. Juvenile idiopathic arthritis subtypes[3 6 w6]

Categories	Characteristics	% of total	Onset age	Sex ratio (F:M)	Relative risk (European vs. non-European)
Systemic juvenile idiopathic arthritis	Arthritis and daily fever ≥3 days, accompanied by at least one of the following: evanescent (non-fixed) erythematous rash, generalised lymph node enlargement, hepatomegaly or splenomegaly (or both), serositis	4-17	Throughout childhood	1:1	2.5
Oligo-arthritis:	Arthritis affecting 1-4 joints during the first 6 months of disease	27-60	Early childhood (peak 2-4 years)	5:1	
Persistent	Arthritis affecting ≤4 joints throughout the disease course	40			3.3
Extended	Arthritis affecting >4 joints after the first 6 months of disease	20			6.0
Poly-arthritis:	Arthritis affecting ≥5 joints during the first 6 months of disease				
Rheumatoid factor positive	Two or more positive tests for rheumatoid factor at least 3 months apart	2-7	Late childhood or adolescence	3:1	0.8
Rheumatoid factor negative	Tests for rheumatoid factor negative	11-30	Early peak 2-4 years and late peak 6-12 years	3:1	3.9
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in first degree relative	2-11	Late childhood or adolescence	1:0.95	6.4
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain (or both), HLA-B27 antigen positive, onset in boy over 6 years old, acute anterior uveitis, HLA-B27 associated disease* in first degree relative	1-11	Early peak 2-4 years and late peak 6-12 years	1:7	1.7
Undifferentiated arthritis	Arthritis that fulfils criteria in no specific category or meets criteria for more than one category	11-21			

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

HOW IS THE DIAGNOSIS MADE?

No conclusive laboratory tests are available for the diagnosis of juvenile idiopathic arthritis, so a good history and physical examination are important.[7] The diagnosis is made by excluding joint problems with a discernable cause. Box 1 lists causes of joint pain in children.

BOX 1. Differential diagnosis of joint problems in children[8]

Arthritis*

Infective and reactive: Lyme disease, viral infection, mycoplasma infection, post-streptococcal reactive arthritis

Juvenile idiopathic arthritis

Connective tissues disorders: systemic lupus erythematosus, dermatomyositis, systemic sclerosis

Systemic vasculitis: Henoch-Schönlein purpura, Kawasaki's disease, polyarteritis nodosa

Other: haemophilia, immunodeficiency (including periodic fever syndromes), sarcoidosis, inflammatory bowel disease

Mechanical and degenerative causes†

Trauma: accidental and non-accidental

Hypermobility

Avascular necrosis including Perthes' disease, Osgood- Schlatter's disease, Scheuermann's disease

Slipped upper femoral epiphyses

Anterior knee pain including chondromalacia patallae

Non-organic causes†

Idiopathic pain syndromes: diffuse or localised (reflex sympathetic dystrophy)

Benign nocturnal idiopathic limb pains (growing pains)

Psychogenic causes

Miscellaneous causes‡

Osteomyelitis

Tumours: malignant (leukaemia, neuroblastoma) or benign (osteoid osteoma, pigment villonodular synovitis)

Endocrine and metabolic abnormalities: rickets, diabetes, hypophosphataemic rickets, hypothyroidism or hyperthyroidism

Genetic disorders: skeletal dysplasias, mucopolysaccharidoses, collagen disorders (Ehlers-Danlos syndrome, Stickler's syndrome)

*Joint(s) show (or mimic) signs of inflammation: redness, swelling, heat, pain, loss of function
†Most likely cause in otherwise well patients with joint pain but no swelling (except for trauma)
‡Most likely cause in patients with overall malaise in addition to joint problems

History

After queries about joint pain and swelling (including previous episodes), ask patients and parents about morning stiffness that lasts for more than 15 minutes but improves

during the day.[7 9] Parents, other family members, or teachers may have noticed problems with, for example, walking, running, climbing stairs, standing up, writing, or sleeping. The child might need help with daily activities that were previously performed independently. Also ask about autoimmune disease in relatives, and in suspected psoriatic arthritis and enthesitis related arthritis (table 1) ask about specific family history.[3 w7] Lastly, ask about any systemic features such as rash or intermittent pyrexia (see table 1).

Physical examination

Examine all joints for pain or tenderness, swelling, limited movement, decreased strength or muscle atrophy, and bony deformity.[7 9] Observe the child while walking, standing up, sitting down, or climbing on to the examination table. In a general examination look for features such as lymphadenopathy, organ enlargement, systemic rashes, nail abnormalities, psoriatic rash, or enthesitis. Always measure growth parameters. Eyes should be checked by an ophthalmologist for uveitis.

Clinical features

Clinical features strongly depend on the subtype and differ in age at onset of disease, number and location of joints involved, disease course, presence of antinuclear antibodies or rheumatoid factor, presence of chronic or acute uveitis, presence of systemic features, and HLA allelic associations (table 1).[w8] Patients with oligo-arthritis (one to four joints affected in first six months of disease) usually present with arthritis in the knees, ankles, or elbows rather than the hips. Chronic anterior uveitis develops in a fifth of these patients and most will be antinuclear antibody positive.[10 w8] Most patients with poly-arthritis (five or more joints affected in first six months) present with symmetrical arthritis in large and small joints and less commonly with uveitis.[w8] Onset may be acute or insidious. Systemic disease is characterised by fever with one or more daily spikes for at least three days. As well as arthritis, which affects a variable number of joints, there are systemic features (table 1).[3] Arthritis may start weeks or even years after the onset of systemic features and can present as a single episode or become persistent. Patients with enthesitis related arthritis can present with oligo-arthritis or poly-arthritis of the large or small joints as well as enthesitis (table 1).[3 w8] Patients who also have psoriasis, a history of psoriasis in a first degree relative, nail pitting, or dactylitis will probably have psoriatic arthritis unless rheumatoid factor is positive.[3 w8]

Further investigations

Other investigations for all subtypes include laboratory tests—a full blood examination, inflammatory markers (erythrocyte sedimentation rate, C reactive protein), and autoimmune markers (rheumatoid factor, HLA B27, and antinuclear antibodies)—and imaging studies.[7 9] Radiography can detect narrowing of the joint spaces or erosions and might

show maturation differences or growth abnormalities in bones from an early stage.[w9] Magnetic resonance imaging studies can also show inflamed synovium and increased joint fluid.[w9]

Referral

Refer all children with suspected or confirmed juvenile idiopathic arthritis to a paediatric rheumatologist as soon as possible to prevent delay in treatment. A cohort study of 128 patients with juvenile idiopathic arthritis and a placebo controlled trial showed that time to treatment is an important factor in response to treatment.[11 12]

HOW DOES JUVENILE IDIOPATHIC ARTHRITIS AFFECT PATIENTS?

Patients with active arthritis have pain, fatigue, and limitation in performing daily activities, but the degree to which patients are affected differs. The course of the disease is related to the subtype—persistent oligo-arthritis is generally the mildest form and systemic the most severe form. When disease is not completely controlled, long term local or systemic complications can occur, depending on the subtype, severity of the disease, and the treatment given. Case-control studies show that long term localised joint inflammation can lead to flexion deformities, damage of cartilage and bone, and bony overgrowth that results in limb length discrepancies.[13 14] Observational studies show that overall growth can be affected by the disease itself and other factors, such as use of corticosteroids.[w10-w12] Chronic inflammation can cause anaemia.[w13] Uveitis, which occurs in 5-20% of patients, most commonly in the oligo-articular subtype, can be asymptomatic and can lead to cataracts and even blindness.10 Regular ophthalmology checks are indicated. The systemic subtype is associated with the most serious morbidity and even mortality.[15] Conditions associated with this subtype include amyloidosis and macrophage activation syndrome.[15 w14]

Despite improvements in treatment, a review published last year showed that a large proportion of children with juvenile idiopathic arthritis still have active disease throughout childhood and enter adulthood with active disease.[16] Several clinical studies have shown that patients with active disease have low health related quality of life[17 18]—the disease affects their physical, emotional, and social wellbeing. A review found that affected children have lower self esteem, are more likely to have behavioural problems than their peers, and are limited in their social lives because of mobility problems and pain.[w15] The patient's family is also affected—the disease has an emotional impact on parents and limits family activities. Fortunately, several studies have shown that family cohesion is not affected.[17 w15]

HOW IS JUVENILE IDIOPATHIC ARTHRITIS TREATED?

Because there is currently no cure for juvenile idiopathic arthritis, the goal of treatment is clinical remission (complete absence of disease).[2 7 w16] Treatment aims to control the inflammatory process by decreasing the number of actively affected joints and to improve the quality of life. A validated set of response variables is used to measure the response to treatment in patients enrolled in clinical trials (box 2).[19] Patients are considered to be in remission if they have had no active arthritis, fever, rash, serositis, or generalised lymphadenopathy attributable to juvenile idiopathic arthritis; no active uveitis; a normal erythrocyte sedimentation rate or C reactive protein; and no disease activity as assessed by a doctor for the past six months.[20]

BOX 2. Juvenile idiopathic arthritis core set of response variables[19]

- Global assessment of the disease activity by the doctor using a visual analogue scale (VAS) (range 0-100 mm, 0 best score)
- Childhood health assessment questionnaire (CHAQ) (range 0-3, 0 best score) used by the patient or parent (measures functional ability)
- Global assessment of wellbeing by the patient or parent using a visual analogue scale (range 0-100 mm, 0 best score)
- Number of joints with active arthritis
- Number of joints with limited movement
- A laboratory marker of inflammation—erythrocyte sedimentation rate or C reactive protein

Patients have responded if at least three variables have improved by 30% (50%, 70%, 100%) and no more than one variable has worsened by more than 30% (ACR pediatric 30%, 50%, 70%, or 100% response)[19]

Old versus new approach to treatment

In the past, juvenile idiopathic arthritis was treated with non-steroidal anti-inflammatory drugs (NSAIDs), with delayed addition of synthetic disease modifying anti-rheumatic drugs (DMARDs) or systemic corticosteroids (or both), and lastly biologic DMARDs. However, accumulating evidence from cohort studies and trials has shown that a more aggressive approach to disease control, with earlier introduction of DMARDs, prevents or minimises long term sequelae of the disease.[11 12 16] Existing guidelines on care have not been revised to include such advice but do advocate "tight" clinical control.[2 w16]

Drug treatment

Up to date international guidelines are currently lacking. The British Paediatric Rheumatology Group provided guidelines for the management of childhood arthritis in 2001,[21] but because treatment is changing rapidly, this guideline needs revision. A recent

guideline from the Royal Australian College of General Practitioners focuses on NSAID treatment only.[9] New recommendations for the treatment of juvenile idiopathic arthritis were presented at the American College of Rheumatology 2010 November meeting but have not been published yet. They are based on studies also mentioned in this review and on expert opinions when evidence is lacking. The treatment modalities we describe are based on randomised controlled trials, case series, and cohort studies. The figure outlines a simplified approach to treatment.

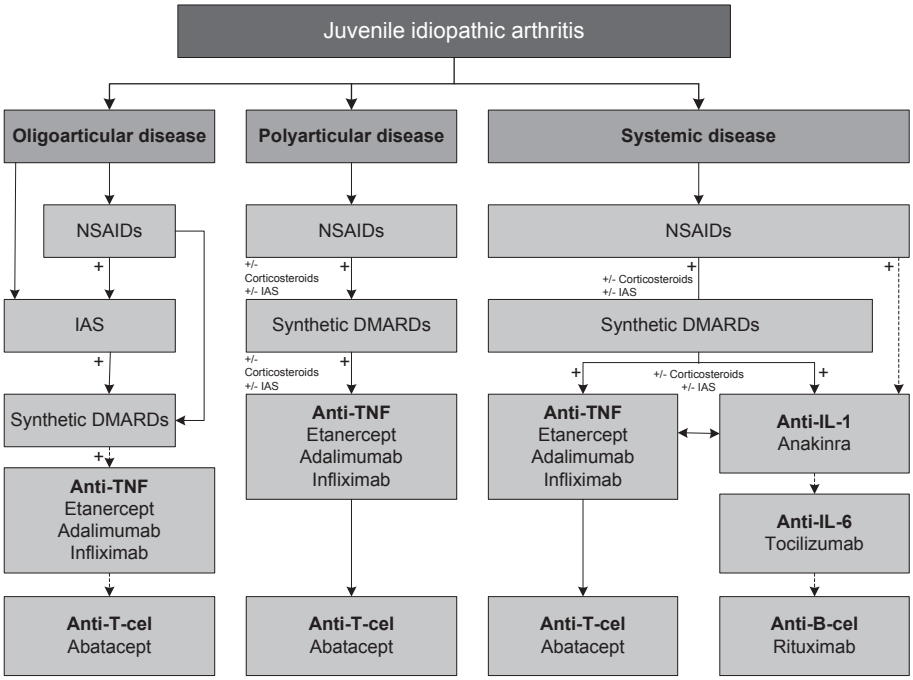

FIGURE. Simplified approach to treatment of patients with juvenile idiopathic arthritis.
Steps often rapidly succeed one another or are combined.
DMARDs, disease modifying anti-rheumatic drugs; IAS, intra-articular steroids; IL, interleukin; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor

Non-steroidal anti-inflammatory drugs

During diagnosis, while other causes of arthritis are being excluded, most patients are given NSAIDs. These drugs relieve pain usually within a few days and do not, as more aggressive treatments can, interfere with the disease course in case of misdiagnosis. Several NSAIDs are used, and none has proved to be superior to another.[22] Recent randomised trials found that the newer cyclo-oxygenase-2 inhibitors (rofecoxib, celecoxib, and meloxicam) were no more effective or safer than the most commonly prescribed NSAID, naproxen.[w17-w19] More than half of patients achieved an ACR paediatric 30 re-

sponse (box 2) after three months of NSAID monotherapy, an NSAID added to a stable dose of a synthetic DMARD, or biologic DMARD treatment, although these responses were not compared with placebo.[w17-w19]

Corticosteroids (intra-articular and systemic)

Children with oligo-articular disease are often given NSAID monotherapy, intra-articular corticosteroids alone, or a combination of both. Intra-articular corticosteroids are increasingly being used, and earlier in the disease course. In a retrospective study of 121 injected joints, all joints responded within one week, and after one year 52% were still in remission.[w20] A randomised double blind trial confirmed this rapid and long lasting effect and showed that triamcinolone hexacetonide is superior to triamcinolone acetonide (85% of joints still in remission after one year) and should be the drug of first choice.[23] Skin atrophy at the injection site occurred in 2.3% of the treated joints.[23] The systemic absorption of triamcinolone, which peaks at eight hours after injection, is usually not clinically relevant, although cases of Cushing's syndrome and transient increases in blood glucose in patients with diabetes have been reported after intra-articular injection.[w21 w22] The long term use of systemic corticosteroids has declined because of side effects, particularly reduced growth and bone health.[w12] These drugs are mainly used while waiting for DMARDs to take effect and in patients with severe systemic or poly-articular juvenile idiopathic arthritis unresponsive to treatment with synthetic and biologic DMARDs.[22 w7]

Synthetic disease modifying anti-rheumatic drugs

Patients with a definite diagnosis of poly-articular disease or oligo-articular disease refractory to intra-articular steroids are candidates for second line agents (DMARDs). Table 2 lists the typical doses, side effects, and contraindications of such drugs used in juvenile idiopathic arthritis.

Methotrexate is the most widely used and first choice synthetic DMARD. A randomised placebo controlled trial (127 patients), a randomised placebo controlled crossover trial (43 patients with extended oligo-articular arthritis), and a dose finding trial (80 patients, mostly unresponsive to low dose methotrexate) found it to be effective—with significant reductions in active and limited joint counts, and high overall improvement—in patients with poly-articular and oligo-articular extended disease.[24 w23 w24] However, it produced no overall improvement in systemic disease—the most difficult subtype to treat.[24] It is unclear how long after remission methotrexate should be withdrawn; a recent randomised clinical withdrawal trial found no differences in relapse rates in patients who continued the drug for six or 12 months (57% v 56%) after induction of remission.[w25A] randomised placebo controlled trial (69 patients) also found sulfasalazine to be effective in the management of juvenile idiopathic arthritis, with a higher response rate than placebo (69% v 45%) after 24 weeks of treatment.[25] However, the drug was not well tolerated, and

TABLE 2. Synthetic disease modifying antirheumatic drugs

Agent	Dose*	Contraindication	Common side effects
Methotrexate (Emthexate, Metoject)	10-15 mg/m2 once weekly orally or subcutaneously (maximum 25 mg/m2)	Liver dysfunction, kidney dysfunction, immunodeficiency, bone marrow dysfunction, active infection, pregnancy, breast feeding	Gastrointestinal symptoms (nausea, vomiting, anorexia); less commonly transient rises in liver transaminases and haematological disturbances
Sulfasalazine (Salazopyrin)	50 mg/kg orally divided into 2 or 3 doses a day (maximum 2000 mg/day)	Salicylate hypersensitivity, systemic disease	Gastrointestinal symptoms, allergic reactions; less commonly, myelosuppression
Leflunomide (Arava)	<20 kg: 100 mg orally for 1 day and then 10 mg every other day;20-40 kg: 100 mg orally for 2 days and then 10 mg/day;>40 kg: 100 mg orally for 3 days and then 20 mg/day	Severe immunodeficiency, bone marrow dysfunction, serious infection, liver dysfunction, severe hypoproteinaemia, pregnancy, breast feeding	Gastrointestinal symptoms, rash, allergic reactions, headache, reversible alopecia; less commonly, transient rises in liver transaminases, haematological disturbances; can be teratogenic
Ciclosporin A (Neoral)	3-7 mg/kg daily orally or intravenously	Renal impairment, uncontrolled hypertension, uncontrolled infections, malignancy	Hypertension and nephrotoxicity; depletion of calcium and magnesium can be associated with muscle cramping; hirsuitism and gum hyperplasia often reported at higher doses

*m2 refers to body surface; kg refers to body weight.

nearly a third of patients discontinued treatment.[25] With the development of newer biologic DMARDs, the use of sulfasalazine has decreased. In a relatively small randomised controlled trial, leflunomide was found to be less effective than methotrexate but with similar adverse event rates.[26] There are no controlled studies of ciclosporin A in juvenile idiopathic arthritis, although small case series show a beneficial effect in severe systemic disease.[w26 w27] A large observational study of 329 patients treated with ciclosporin A found a 9% complete response rate; most patients discontinued the drug because of inefficacy.[w28] Case series have shown that ciclosporin A might be effective in macrophage activation syndrome.[w29 w30] The use of leflunomide and ciclosporin A in juvenile idiopathic arthritis is limited. Other synthetic DMARDs (auranofin, penicillamine, and hydroxychloroquine) have not been shown to have a significant therapeutic advantage over placebo, in contrast to findings in adult patients with rheumatoid arthritis.[w31 w32]

Biologic disease modifying anti-rheumatic drugs

With the introduction of biologic DMARDs (also known as biologics or biologicals) the goal has shifted from reducing inflammation to "switching off" the autoimmune system

by targeting inflammatory cytokines. Table 3 lists the biologic DMARDs currently available or under investigation for juvenile idiopathic arthritis.

Tumour necrosis factor is a proinflammatory cytokine that plays a central role in the pathogenesis of juvenile idiopathic arthritis.[w33] In systemic disease, interleukin 1 (a proinflammatory cytokine synthesised by fibroblasts in the synovium and macrophages) and interleukin 6 (concentrations of which correlate with fever, disease activity, and platelet counts) are also thought to be important.[w33-w35] If inhibition of these cytokines is not sufficient, other drugs aimed at T cell blockade and B cell depletion are available.[w36] Only etanercept, adalimumab, and abatacept have been approved by the European Medicines Agency and the Food and Drug Administration for the treatment of juvenile idiopathic arthritis after testing in placebo controlled withdrawal trials.[27-29] These trials are designed so that all patients start the drug in an initial open label part of the trial. Those with an ACR paediatric 30 response to treatment (box 2) enter a double blind study and are randomly assigned to receive placebo or the biologic DMARD until the disease flares. The response rates (ACR paediatric scores) reported from these trials come from the open label phase and represent the initial responders.[w37] Results from the randomised blinded phase are presented as flare rates. This design is used in paediatric rheumatology trials to minimise the consequences of placebo treatment.

Other biologic DMARDs are prescribed off label, although some (infliximab, anakinra, tocilizumab) have been tested in patients with juvenile idiopathic arthritis in placebo controlled withdrawal trials (table 3).[w38-w40] Choice of biologic DMARD is based on effectiveness, safety, route of administration, and arthritis subtype.

Etanercept was the first and for a long time the only registered biologic DMARD for the treatment of juvenile idiopathic arthritis; 74% of patients previously resistant to other drugs, including methotrexate, met the ACR paediatric 30 target after three months in the placebo controlled withdrawal trial.[27] Many observational studies have provided data on safety and response; the drug seems to be well tolerated and effective.[w41-w46] It is the most commonly prescribed biologic DMARD for patients with this disease, followed by adalimumab. A prospective registry study found that etanercept reduced disease activity and improved quality of life in all aspects affected by the disease.[17] A health related quality of life study of abatacept showed similar results.[w47] A placebo controlled withdrawal trial showed that abatacept was effective in patients for whom anti-tumour necrosis factor was not effective (ACR paediatric 30 response in 39%), thereby providing a valuable alternative treatment.[29] The treatment of systemic disease is challenging.[15] In a controlled clinical withdrawal trial and case series anakinra seemed to be better than etanercept in reducing systemic symptoms.[15 w38 w48-w50] Other biologic DMARDs (table 3) have shown promising results in clinical trials or case series. No head to head trials on choice of biologic DMARD exist for these patients. Today, most experts favour anakinra

TABLE 3. Biological disease modifying antirheumatic drugs currently available or under investigation for juvenile idiopathic arthritis

Agent	Action	Dose*	Used in subtypes	Other paediatric indications (approved or off label)
TNF-α blocking agents				
Etanercept (Enbrel)	TNF-α receptor fusion protein	0.4 mg/kg twice weekly SC or 0.8 mg/kg weekly SC (max 50 mg/week)	All patients with polyarticular course and seldom in oligoarticular persistent†	Plaque psoriasis
Adalimumab (Humira)	Human monoclonal anti-TNF antibody	<30 kg: 20 mg every two weeks SC; >30 kg: 40 mg every two weeks SC	All patients with polyarticular course‡	Crohn's disease, ulcerative colitis, uveitis
Infliximab (Remicade)	Chimeric murine-human monoclonal anti-TNF antibody	6-10 mg/kg IV at 0, 2, and 6 weeks, then every 4-8 weeks	All patients with polyarticular course†	Crohn's disease, ulcerative colitis, plaque psoriasis, uveitis
T cell co-stimulation modulator				
Abatacept (Orencia)	T cell co-stimulation modulator	10 mg/kg IV at 0, 2, and 4 weeks (maximum 1000 mg), then every 4 weeks	All patients with polyarticular course¶	
Interleukin 1 blocking agents				
Anakinra (Kineret)	IL-1 receptor anatagonist	1-2 mg/kg daily SC (maximum 100 mg)	Systemic disease†	Cryopyrin associated periodic syndrome
Rilonacept (Arcalyst)	IL-1 receptor-IL1RacP-FC fusion protein	Loading dose of 4.4 mg/kg SC (maximum 160 mg), then weekly doses of 2.2 mg/kg	Systemic disease**	Cryopyrin associated periodic syndrome
Canakinumab (Ilaris)	Human IL-1β antibody	<40 kg: 2-4 mg/kg every 8 weeks SC; >40 kg: 150-300 mg every 8 weeks SC	Systemic disease**	Cryopyrin associated periodic syndrome
Interleukin 6 blocking agent				
Tocilizumab (RoActemra)	IL-6 receptor antibody	<30 kg: 12 mg/kg every 2 weeks SC; >30 kg: 8 mg/kg every 2 weeks SC	Systemic disease††	
B cell depletion agent				
Rituximab (Rituxan)	Chimeric anti-CD20 monoclonal causing B cell depletion	<40 kg: 2 doses of 500 mg IV 2 weeks apart; >40 kg: 2 doses of 1000 mg IV 2 weeks apart	Systemic disease**	Systemic lupus erythematosus, B cell non-Hodgkin's lymphoma

Abbreviations: . IL=interleukin, IV=intravenous, TNF=tumour necrosis factor, SC=subcutaneous.

*kg refers to body weight.

Placebo controlled withdrawal trials published for:

†Subtypes: systemic, oligoarticular extended, and polyarticular (rheumatoid factor positive and negative).

‡Patients with a polyarticular course (any subtype).

¶Subtypes: systemic (without systemic manifestations), oligoarticular extended, and polyarticular (rheumatoid factor positive and negative).

**No randomised trials (yet) published in juvenile idiopathic arthritis.

††Systemic subtype only.

when systemic features are prominent, but the timing of this treatment is debatable.[30] More studies on management of systemic arthritis are needed.

The most commonly encountered adverse events of biologic DMARDs are local reactions at injection sites and opportunistic infections.[31 w51] Most injection site reactions resolve as a result of tolerance. Consult a paediatric rheumatologist if the drug has to be discontinued because of a serious infection. Less commonly encountered but important adverse events are neurological or neuropsychological disorders, new onset autoimmune diseases, and cancer. The most common cancers reported related to anti-tumour necrosis factor treatment are hepatosplenic T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukaemia, although there is no convincing evidence of an increased risk.[31 w52 w53] Similarly, although safety studies with long term follow-up have

BOX 3. Safety and monitoring of synthetic* and biological disease modifying antirheumatic drugs

Overall recommendations

Do not start treatment in patients with an active infection, current or previous tuberculosis, immunodeficiency, cancer, or precancerous state[w54]

In each infectious episode during treatment, consider the need to discontinue the drug temporarily[w54]

Perform regular check-ups with full blood counts and liver and kidney function tests[w54]

Be aware of adverse events, including neurological and neuropsychological disorders, new onset autoimmune diseases, and cancers[w54]

Avoid live (attenuated) vaccines until more data are available[w55 w56]

Killed (or inactivated) vaccines are safe, although the immune response may be suboptimal and boosters may be needed[w57-w59]

Yearly influenza vaccination is recommended[w54]

Give any susceptible patient exposed to varicella specific immunoglobulin and aciclovir at first sign of infection; consider vaccination before starting disease modifying antirheumatic drugs[w54]

Drug specific recommendations

Methotrexate

Give folate supplements 24-48 hours after starting methotrexate to reduce the gastrointestinal and hepatic side effects[w60]

In higher doses parenteral application is recommended because of better bioavailability and tolerability[w61]

Leflunomide and ciclosporin A

Measure blood pressure regularly[w54]

Infliximab

Monitor for acute hypersensitivity reactions until two hours after infusion[w54]

Give methotrexate concomitantly to prevent immunogenicity[w62]

*Applies only to synthetic DMARDs that affect the immune system (methotrexate, leflunomide, ciclosporin A)

shown new onset of the above complications in patients taking biologic DMARDs, we have insufficient data to compare incidence rates in patients taking biologic DMARDs with those in patients not taking biologic DMARDs.[w41-w46] If one of these conditions is suspected in a patient taking a biologic DMARD or other immunosuppressive drug, consult the treating paediatric rheumatologist immediately to discuss discontinuing the drug. Box 3 provides recommendations for safety and monitoring of DMARDs.

Other treatments

Depending on the subtype and severity of disease, the British Society for Paediatric and Adolescent Rheumatology standards of care recommends regular checks by a paediatric rheumatologist, ophthalmologist, dermatologist, orthopaedic surgeon, orthodontist, general practitioner, psychologist, and physiotherapist or occupational therapist. The idea is that a well chosen multidisciplinary team will enable the best possible care.[2]

A Cochrane review has shown that physiotherapy is important to maintain normal muscle and joint function.[w63] Rehabilitation—using heat or cold treatment, massage, therapeutic exercise, and splints—is crucial to returning to activities of daily living again once these have been limited by disease.[9] The British Society for Paediatric and Adolescent Rheumatology standards of care guideline also recommends psychological therapy and education.[2]

Supplements may be needed to prevent certain side effects of treatment. During corticosteroid treatment patients are at increased risk of osteoporosis and osteopenia. Several studies, including a randomised clinical trial, found a small but significant beneficial effect of calcium and vitamin D supplements on bone mineral density.[w64 w65] Children using methotrexate might benefit from folic acid supplements. Although evidence that weekly folic acid reduces methotrexate related adverse effects in children is weak, studies in adults with rheumatoid arthritis have shown significant effects.[w66 w67]

Autologous stem cell transplantation was used in autoimmune diseases before biologic agents were available, and several patients with juvenile idiopathic arthritis have been successfully transplanted.[w68 w69] However, because of the risks involved (9% transplant related mortality) and relatively high relapse rates (>30%), this treatment is reserved for patients who are resistant to combinations of synthetic DMARDs, corticosteroids, and biologic DMARDs and who have severe, debilitating, and potentially fatal disease.

WHAT WILL THE FUTURE HOLD?

Despite the lack of a cure, biologic DMARDs have provided a better quality of life for many patients with juvenile idiopathic arthritis who were previously refractory to treatment. In addition, the current trend of early aggressive treatment has improved long-term out-

comes. However, a proportion of patients still have ongoing active disease and associated long term sequelae that limit daily life.[w70] Individual children must be managed according to subtype, severity of disease, and prognostic factors. Research into biomarkers and genetic markers of disease subtype, as well as advances in radiographic imaging, may one day provide earlier diagnosis, better monitoring of disease activity, and more tailored treatments. Outcomes improve with earlier disease control, and trials to investigate the efficacy of various treatments (combining different drugs according to different time schedules) are under way.[w71-w73] The new biologic DMARDs — targeted at interleukins 1 and 6, T cells, and B cells — have shown promising results and might improve treatment for specific patients groups. Disease registries are important sources of data from large patient groups. They can be used to compare different outcomes of treatments, while accounting for patient and disease characteristics, disease course, and occurrence of adverse events during (multiple) treatments over long periods. Registry data provide a real life picture of patients as treated by their doctor. Initiatives to combine registries have begun in Europe and the United States and should help us answer questions on the long term safety of biologic DMARDs. A worldwide consolidated juvenile idiopathic arthritis registry would be ideal. Hopefully, these efforts will result in more choice of effective and safe drugs and an optimal treatment strategy for each patient. The ultimate goal is clinical remission off drugs that could be considered as a "cure."[3]

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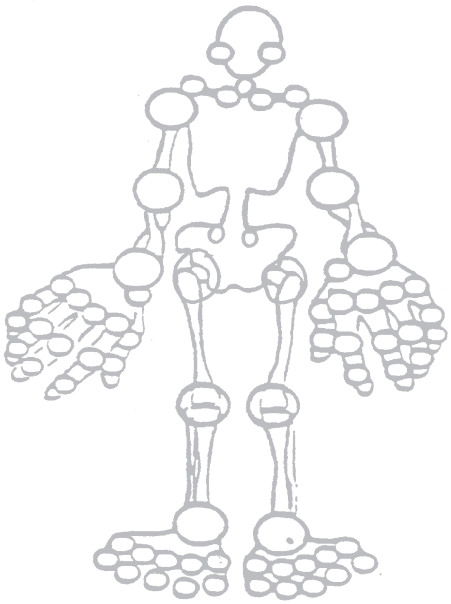
CHAPTER 2.2

Efficacy of biologic agents in JIA: a systematic review using indirect comparisons



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ABSTRACT

Objective: During the last decade the availability of biologic agents for the treatment of juvenile idiopathic arthritis (JIA) increased substantially. Because direct head-to-head trials comparing biologics are lacking, choosing between these agents is often not evidence based. In order to provide some scientific guidance, we indirectly compared the short-term efficacy of biologic agents.

Methods: In a systematic review, all available efficacy data from randomized controlled trials performed in JIA were retrieved. The following biologics were included: etanercept, adalimumab, infliximab, abatacept, anakinra, rilonacept, canakinumab and tocilizumab. Indirect between-drug comparisons (based on the Bucher's method) were conducted only if trials were comparable with regard to design and patients' characteristics related to treatment outcome.

Results: A total of 11 trials evaluated biologic agents in JIA; for five trials no match for an indirect comparison could be found because of differences in design and patient characteristics. The remaining six trials could be divided into two networks of evidence. Network one included three withdrawal trials that evaluated etanercept, adalimumab and abatacept in patients with poly-articular course JIA (any JIA onset category) and a mean disease duration of 3.9-5.8 years. Indirect comparisons identified no statistically significant differences in short-term efficacy between these agents. However, considering the fact that the etanercept treated patient had slightly longer disease duration prior to inclusion and a high percentage of systemic JIA patients were included (33%), etanercept seemed better in preventing disease flares than adalimumab (RR for disease flare etanercept vs. adalimumab 0.59, 95% CI 0.28-1.24). Also abatacept seemed superior to adalimumab (RR for disease flare abatacept vs. adalimumab 0.64, 95% CI 0.34-1.23), especially since 17% of abatacept treated patients were previously unresponsive to TNF-inhibitors. Network 2 indirectly compared anakinra, tocilizumab and canakinumab in systemic JIA and no differences between these agents could be identified. Slightly more patients achieved modified ACRpedi30 response with canakinumab versus tocilizumab (RR 2.44, 95% CI 0.81-7.37), though this difference was not significant.

Conclusions: The short-term efficacy of etanercept, adalimumab and abatacept seemed similar for poly-articular course JIA and anakinra, canakinumab and tocilizumab seemed similar for systemic JIA. Because of the observed differences between trials, head-to-head trials comparing biologic agents directly are highly needed. 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.

INTRODUCTION

Since 1999, the treatment of juvenile idiopathic arthritis (JIA) has been extended with a new category of drugs: biologic agents that target different cytokines and different steps in the immune response. Etanercept, a tumour necrosis factor (TNF)-alpha receptor antagonist, was the first biologic approved for the treatment of poly-articular JIA.
Until now, also infliximab (anti-TNF-alpha antibody), adalimumab (anti-TNF-alpha antibody), anakinra (interleukin (IL)-1 receptor antagonist), canakinumab (anti-IL-1 antibody), rilonacept (IL-1 receptor antagonist), tocilizumab (IL-6 receptor antibody), and abatacept (selective T-cell co-stimulation modulator) are available options or under investigation for the treatment of JIA. It is likely that, in the future, this number of agents will expand even further. Physicians involved in the treatment of JIA nowadays face this increasing number of biologic treatment options and choosing between these treatments is often difficult.
The efficacy of each agent has been described in one or more randomized controlled trials (RCTs), but head-to-head trials comparing agents directly are still lacking. A few studies have compared the short-term efficacy between biologic agents in RA patients using indirect treatment comparisons.[1-6] This technique allows to compare two biologic agents indirectly (i.e. trial comparing treatment A vs. comparator C and treatment B vs. comparator C results in a comparison of A vs. B), while preserving the randomization of the originally assigned patient groups.[2, 7] Efforts to indirectly compare these agents in JIA are to our knowledge still lacking.
We therefore conducted a systematic review and analysed the different RCTs of biologic agents in JIA with regard to their design and patients' characteristics, and, where possible, compared the efficacy between different biologic agents indirectly. Eventually we hope that these results will guide the treating physicians in their biologic treatment choices for JIA.

PATIENTS AND METHODS

Systematic search and data extraction

A systematic search on Pubmed, Embase, and Cochrane clinical trials was performed using the terms: "juvenile idiopathic arthritis" AND "randomized 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 supplementary files 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 (ACR meeting, EULAR and PRES) were searched.

We aimed to include the following studies: RCTs with data on efficacy (disease flare, American College of Rheumatology (ACR) paediatric response, or inactive disease), comparing a biologic agent (i.e. etanercept, adalimumab, infliximab, abatacept, anakinra, tocilizumab, canakinumab, certolizumab, golimumab, rituximab, or rilonacept) versus control treatment (placebo, synthetic disease modifying drugs (sDMARD) or second biologic agent), and including patients with JIA.

Two authors (M.O. and J.A.) independently selected the studies from the search and extracted the following information: design of trial, inclusion and exclusion criteria, medication regimens (including concomitant medication regimens), baseline patient and disease characteristics, number of dropouts, and efficacy results during the double-blind phase. Corresponding authors and involved pharmaceutical industries were contacted for any missing data in the publications. The trial quality was assessed independently with the use of the Jadad criteria, a five-point score that appraises the quality of trial reporting with regard to the description of randomization, double-blinding, and withdrawals and dropouts.[8] If scoring was not unanimous, scoring was discussed with a third person (L.S.). A total of 524 potentially relevant citations were identified. Figure 1 shows the flow of included studies.

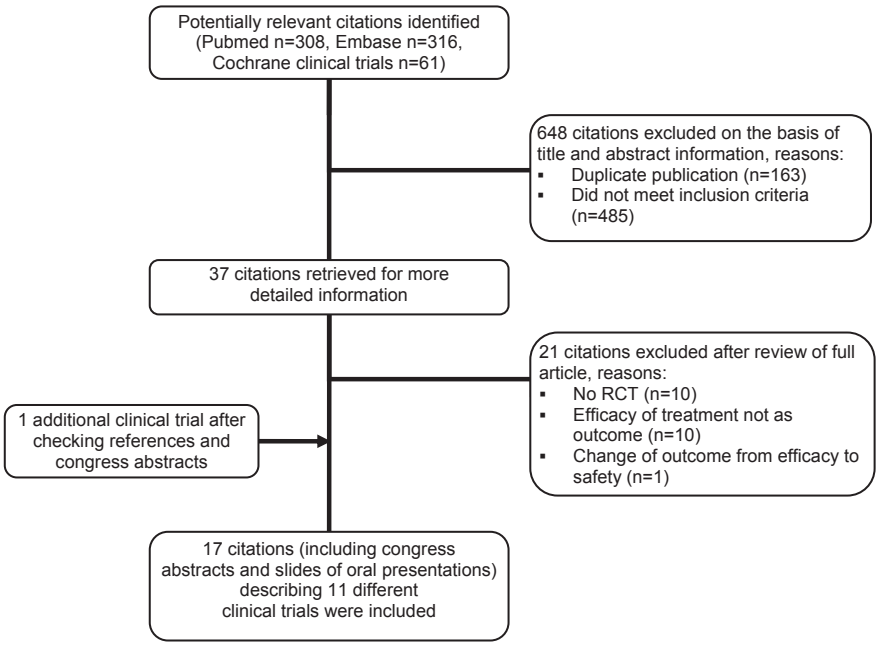

FIGURE 1. Flow of included studies

Trial design

In the field of paediatric rheumatology, in general, two different types of clinical trials are conducted. The randomized placebo-controlled withdrawal trial design (called "withdrawal trial") was the first design used for trials that evaluated biologic agents in JIA. It consists of an open-label lead-in phase where all patients included receive the drug. After this lead-in period, only those patients that respond to treatment enter the double-blind phase and are randomized to remain on the drug or receive placebo. For this withdrawal design the primary outcome chosen is disease flare. This trial design has been developed to overcome some ethical considerations (patients are not withheld from treatment, mainly because time to treatment seems an important factor associated with patients' outcome) and to overcome statistical power difficulties for this rare disease (because, after treatment response, more patients on placebo are expected to flare). Besides this withdrawal design, the "classic" randomized controlled design is used. To overcome the above mentioned ethical difficulties, these trials include concomitant treatment with sDMARDs (for example biologic plus methotrexate versus methotrexate only), short duration of double-blind phase or a rescue regimen.

Outcome

We identified three major outcomes beforehand: percentage of patients with disease flare, percentage of patients achieving an ACR paediatric (ACRpedi) 30 response and percentage of patients achieving inactive disease. These outcomes are based on changes in six "core set" response variables. These variables consist of: 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, global assessment of wellbeing by patients/parents (VAS, range 0-100 mm, 0 best score), number of active joints with arthritis, number of joints with limited motion, and erythrocyte sedimentation rate (ESR). A disease flare is defined as worsening of 30% or more in at least three of the six core set response variables with an improvement of 30% or more in no more than one variable. An ACRpedi30 response (or ACRpedi50/70/90 response) is achieved if three or more variables of the JIA core set improve with at least 30% (or depending on the score 50%/70%/90%) from baseline, with no more than one variable worsening by more than 30%.[9] For the systemic JIA category often a modified ACRpedi30 response is used with the addition of absence of systemic features. Inactive disease is defined as a disease state with no active arthritis, no uveitis, normal ESR and physician's global indicating no disease activity.[10]

Statistical analyses

The relative risks (RR) and corresponding 95% confidence intervals (CI) were calculated for each trial independently. The appropriate statistical method for conducting adjusted

TABEL 1. Description of included studies (for detailed description see supplementary files)

Author (acronym)	Year published	Comparison	Study design	Selected outcome
Lovell[16]	2000	Etanercept vs. placebo	Withdrawal trial*	Disease flare
Ruperto[13]	2007	Infliximab vs. placebo	Randomized placebo-controlled trial	ACRpedi30
Lovell[17]	2008	Adalimumab vs. placebo (stratification according MTX use)	Withdrawal trial*	Disease flare
Ruperto[18]	2008	Abatacept vs. placebo	Withdrawal trial*	Disease flare
Yokota[19-20]	2008	Tocilizumab vs. placebo	Withdrawal trial*	Maintenance of ACRpedi30 response
Ruperto[21]	2009	Canakinumab vs. placebo	Randomized placebo-controlled trial	Modified ACRpedi30 response†
Quartier (ANAJIS)[22]	2010	Anakinra vs. placebo	Randomized placebo-controlled trial	Modified ACRpedi30 response†
De Benedetti (TENDER)[23-27]	2010-2011	Tocilizumab vs. placebo	Randomized placebo-controlled trial	Modified ACRpedi30 response†
Lovell[15]	2011	Rilonacept vs placebo	Randomized placebo-controlled trial	Modified ACRpedi30 response†
Tynjala (ACUTE-JIA)[28-29]	2011	Infliximab+MTX vs. MTX	Randomized open-label trial	ACRpedi70 / Inactive disease
Wallace (TREAT)[14]	2012	Etanercept+tapered prednisone +MTX vs. placebo+MTX	Randomized placebo-controlled trial	ACRpedi70 / Inactive disease

* Only ACRpedi30 responders included in DB phase. For Yokota trial patients with ACRpedi30 response and CRP <5mg/L were included in DB phase only.
† 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 normalization of both ESR and CRP levels.
** Assessment of quality of trial not complete because of insufficient information available (congress abstracts only)
*** Number of patients included in randomized phase

indirect treatment comparisons is the Bucher method (might be applied after random effects meta-analysis) or a meta-regression model.[7] 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: $LnRR'AB = LnRR_{AC} - LnRR_{BC}$

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,

Treatment duration (till evaluation outcome)	Included JIA categories	No. of patients***	Systemic JIA included	Mean disease duration (y)	Previous biologic use	JADAD score for quality
4 months	Poly-articular course JIA	51	33%	5.8	0%	4
14 weeks	Poly-articular course JIA	122	16%	3.9	0%	4
32 weeks	Poly-articular course JIA	133	?	3.8	0%	4
6 months	Poly-articular course JIA	122	19%	3.9	17%	5
12 weeks	Systemic JIA	43	100%	4.7	?	5
15 days	Systemic JIA	84	100%	3.4	?	3**
1 month	Systemic JIA	24	100%	3.7	54%	4
12 weeks	Systemic JIA	112	100%	5.2	?	3**
1 month	Systemic JIA	24	100%	3.1	29% (prior anakinra use)	2**
54 weeks	Early poly-articular course JIA	60	0%	0.16	0%	2
4 months (ACRpedi70) / 6 months (inactive disease)	Early poly-articular course JIA (RF pos and neg categories only)	85	0%	0.42	0%	3

indirect comparisons were conducted only between clinical trials with the same design (withdrawal trial with an open-label lead-in phase vs. randomized controlled trials), and with inclusion of approximately the same patient group with regard to disease duration at baseline and JIA categories included. Adequate methods for the heterogeneity assessment, such as subgroup analysis or sensitivity analysis, were not applicable because of only one trial per treatment. The results of the adjusted indirect comparisons are given as RR with 95% CIs. Two-sided P-values <0.05 were considered statistically significant. Analyses were performed in STATA software (Stata 12, Stata Corporation, College Station, Texas, US). For statistical code in STATA see supplementary files.

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.[11-12]

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 Table A and B of the supplementary files). Four withdrawal trials and seven "classic" randomized controlled trials were included. Overall, eight of the 11 trials met the primary endpoint in favour of the biologic agent. In the randomized placebo-controlled trial by Ruperto et al. no differences between infliximab and placebo with regard to the achievement of an ACRpedi30 response were seen.[13] Also the TREAT trial did not meet its primary endpoint (inactive disease after six months), but the secondary endpoint of achieving an ACRpedi70 response after four months was reached.[14] The rilonacept trial by Lovell et al has not been published yet, however, a congress abstract including the slides of an oral presentation given at the concerning international congress, demonstrated that, after one month, the proportions of patients achieving an ACRpedi30 response were not significantly different between the rilonacept and placebo treated patient groups.[15] Relative to placebo, a greater proportion of patients treated with rilonacept reported no fever or rash during the prior seven days (65% vs. 43%) and the prior 14 days (59% vs. 29%).

Based on the design of the trials, quality of trials, and characteristics of included patients, two networks for indirect comparisons have been 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 poly-articular course JIA (any JIA onset category) and were indirectly compared (Network 1). The fourth withdrawal trial evaluated tocilizumab in systemic JIA patients only and could therefore not be included in the

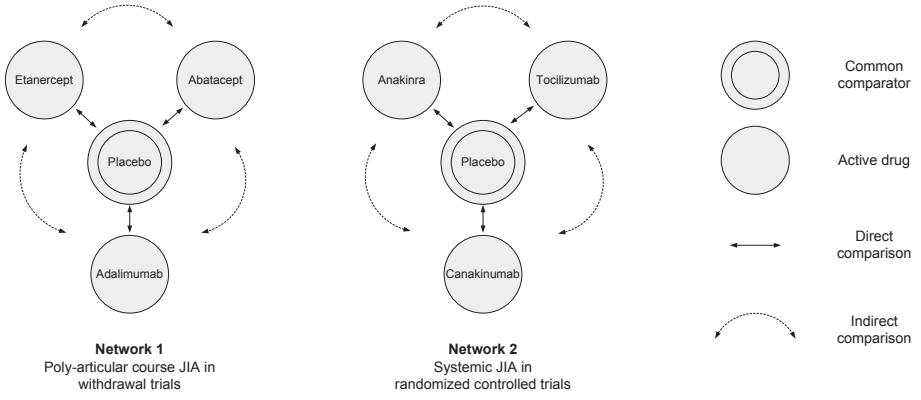

FIGURE 2. Network diagrams of selected indirect comparisons

indirect comparison analysis. Of the seven randomized controlled trials, four included systemic JIA patients only. 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 randomized controlled trial by Ruperto et al. included poly-articular course JIA patients and could not be included in Network 1 (withdrawal trials) and neither in Network 2 (systemic JIA).[13] Finally, two randomized controlled trials included early JIA patients only (after mean disease duration of 0.16-0.42 year). However, because of low trial quality and significant differences in the inclusion of rheumatoid factor positive patients (36% of RF-positive in the TREAT trial versus 2% in the ACUTE-JIA trial) no valid indirect comparisons could be made.[14, 28]

Network 1. Withdrawal trials (including a lead-in phase with active drug)

For the three comparable withdrawal trials the disease duration at baseline varied between 3.8 and 5.8 years, and the mean age at baseline between 10.6 and 12.3 years. The percentage of included systemic JIA patients with poly-arthritis in the adalimumab withdrawal trial was unclear. Inclusion of systemic JIA varied between the etanercept and the abatacept trials (33% and 19% systemic JIA patients included respectively), but inclusion of RF positive patients was similar across all three trials (21%-24%). Previous used biologic medications differed with inclusion of 17% of patients who were previously non-responsive to TNF-alpha antagonists in the abatacept trial compared with none in the etanercept and adalimumab trials. Of the patients that 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 score were comparable between the three trials. Indirect comparisons indicated no differences in efficacy between these three drugs.(Table 2) There seems to be a trend favouring etanercept over adalimumab (RR for a disease flare of etanercept vs. adalimumab was 0.59, 95% CI 0.28-1.24) and a similar trend favouring abatacept over adalimumab (RR for a disease flare of adalimumab vs. abatacept was 1.56, 95% CI 0.81-2.99) however no significance was reached.

Network 2. Randomized placebo-controlled trials in systemic JIA

The three selected randomized placebo-controlled trials compared anakinra, tocilizumab and canakinumab with placebo. The duration of the double-blind phase was 12 weeks for the tocilizumab trial, one 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 drug for the achievement of a modified ACRpedi30 response.(Table 2) Canakinumab seems to be superior to tocilizumab (RR for achieve-

ment of modified ACRpedi30 response of tocilizumab vs. canakinumab was 0.41, 95% CI 0.14-1.23), however, not significant.

TABLE 2. Outcomes of trials and indirect comparisons

Author	Comparison	Outcome	No. of patients included	No. of patients with outcome active drug arm	No. of patients with outcome control arm	RR (95% CI) for outcome
Network 1						
Lovell et al.[16]	Etanercept vs. placebo	Disease flare	51	7 / 25	21 / 26	0.35 (0.18-0.67)
Lovell et al.[17]	Adalimumab* vs. placebo	Disease flare	133	27 / 68	44 / 65	0.59 (0.42-0.82)
Ruperto et al.[18]	Abatacept vs. placebo	Disease flare	122	12 / 60	33 / 62	0.38 (0.22-0.66)
Network 2						
Quartier et al.[22]	Anakinra vs. Placebo	Modified ACRpedi30 response†	24	8 / 12	1 / 12	8.00 (1.17-54.50)
De Benedetti et al.[23, 25-27]	Tocilizumab vs. Placebo	Modified ACRpedi30 response†	112	64 / 75	9 / 37	3.51 (1.97-6.24)
Ruperto et al. [ref]	Canakinumab vs. Placebo	Modified ACRpedi30 response†	84	36 / 43	4 / 41	8.58 (3.35-21.97)

Indirect Comparison	RR (95% CI)	P value
Network 1	*Disease flare*	
Etanercept vs. Adalimumab*	0.59 (0.28-1.24)	0.16
Etanercept vs. Abatacept	0.92 (0.39-2.18)	0.85
Adalimumab* vs. Abatacept	1.56 (0.81-2.99)	0.18
Network 2	*Modified ACRpedi30 response*	
Anakinra vs. Tocilizumab	2.28 (0.31-16.93)	0.42
Anakinra vs. Canakinumab	0.93 (0.11-7.91)	0.95
Tocilizumab vs. Canakinumab	0.41 (0.14-1.23)	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 normalization of both ESR and CRP levels, and in the tocilizumab and canakinumab trials as an ACRpedi30 response together with no fever.

[RR=relative risk; CI=confidence interval]

DISCUSSION

In this systematic review we found that, in JIA, 11 trials compared biologic agents with placebo or sDMARDs, and no trials compared biologics directly. Because these trials differed with regard to design and patient characteristics, not all trials could be included in the indirect comparisons. Two similar networks of trials were identified (poly-articular course JIA (any JIA onset category) in withdrawal trials and systemic JIA only in classic RCTs) in order to make valid indirect comparisons. For poly-articular course JIA, etanercept, adalimumab and abatacept seem equally efficacious in preventing disease flare after response to treatment. Canakinumab, tocilizumab and anakinra seem to have a comparable effect in systemic JIA.

To the best of our knowledge, this is the first effort to indirectly compare the efficacy of biologics in JIA. Indirect treatment comparisons have been performed in rheumatoid arthritis (RA) previously, because also in RA only few trials comparing biologic agents directly have been conducted. The results of the comparisons in RA are not fully decisive, but generally seem to indicate that TNF-inhibitors are more effective than anakinra and etanercept is more effective than other TNF-inhibitors.[4, 30-31] Tocilizumab seems to be more effective in RA than TNF-inhibitors and abatacept.[3, 32] In the present study tocilizumab was only investigated in systemic JIA.

The indirect comparisons in the first network indicated that etanercept, adalimumab and abatacept were equally effective for poly-articular course JIA. However, though no significant differences were found, some arguments might support the existence of differences in efficacy between these biologics. Etanercept tended to be superior to adalimumab, and this effect might be more pronounced considering the fact that in the etanercept trial disease duration before start seemed slightly longer (5.8 years versus 3.8 years) and high percentage of systemic JIA patients were included (33%). In contrast, the observed treatment period was shorter for the etanercept trial compared with the adalimumab trial (4 months vs. 36 weeks).The efficacy of etanercept might thereby be overestimated, because a shorter duration of the trial results in a smaller chance to reach the time-dependent outcome, in this case disease flare. Abatacept seemed superior to adalimumab and equally effective to etanercept. However, the effect of abatacept might be underestimated, because 17% of the patients included in the abatacept trial were non-responders to previous treatment with TNF-inhibitors indicating a more therapy-resistant patient group. Because these results could not be compared with similar analyses or with head-to-head trials including JIA patients, the only feasible comparison is one with data from observational studies performed in JIA. Extensive observational data on etanercept for poly-articular course JIA are available, all showing impressive effects for

both short-term and long-term.[33-34] However, observational studies analyzing adalimumab and abatacept in poly-articular course JIA are scarce.[35-36] Adalimumab seems to be mainly preferred when uveitis is present.[37] A small number of observational studies did compare the effectiveness of etanercept to that of infliximab in poly-articular 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.[38-40] An indirect comparison between etanercept en infliximab could unfortunately not be performed because of trial design dissimilarities.

The second network analysis included trials that investigated IL-1 and IL-6 blockers in systemic JIA. Trials in this network were very comparable and the indirect comparisons found anakinra, canakinumab and tocilizumab to be equally effective for systemic JIA. A possible trend towards favouring canakinumab over tocilizumab has been observed, however, this needs to be confirmed in further studies. 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 systemic JIA patients.[34, 41-42] Many observational studies found anakinra to be highly effective[43-44], but observational studies that evaluate canakinumab and tocilizumab in systemic JIA are still lacking.

Until conclusive differences are established, decisions to choose between biologics in JIA should mainly depend on drug availability, safety (including available data on long-term safety), practical reasons (like interval of injections), and treatment costs. Furthermore, more insight in other features than clinical characteristics, such as cytokine or genetic profiling, related to the treatment response might contribute to this decision making. Focus could be shifted from treatment of the heterogeneous group of all JIA subtypes to tailored patient-specific care.

A review indicated that the National Institute for Clinical Excellences (NICE) prefers direct comparisons in decision making. Even in the absence of direct comparisons, key decisions are still based on information from original trials, rather than on the indirect comparisons available.[45] Head-to-head trials remain needed, however until decisive direct evidence is established, decisions will have to be based on the existing sources. Besides the use of indirect comparisons methods, also observational studies that compare two biologics with the use of propensity score matching can be used.[46] The indirect treatment comparison method has the opportunity to, in contrast to observational studies and meta-analyses, 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 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.[47-48] The strengths and weaknesses in the present study, with regard to these three factors, are discussed below.

All available sources were searched after in order to identify all potentially relevant trials. To minimize publication bias, all registered trials on clinicaltrials.gov were reviewed and no additional trials that were completed could be identified. A trial on rilonacept had to be excluded from the indirect comparisons, because insufficient efficacy data were available despite the fact that corresponding author and involved pharmaceutical industry were contacted.[15]

Quality of trials varied greatly and unfortunately not all trials could be fully assessed, because data had to be extracted from conference abstracts.[49] Earlier trials for registration commissioned by pharmaceutical industries gained best scores, while more recent trials that evaluated treatment strategies in approved biologics performed worst. Lower scores were mainly achieved because of a lack of detailed description of randomization and allocation concealment. Low trial quality of the TREAT trial was one of the reasons to exclude this trial from the indirect treatment 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, though 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 primary response, does not necessarily imply better initial treatment responses.

The biggest challenge for this indirect comparison was fulfilling the similarity assumption, because of the heterogeneity of the disease and the scarcity of trials in paediatric rheumatology. Six trials were found suitable for indirect comparisons performed in two networks of trials that, relying on clinical judgement, were comparable. These two networks consisted of methodologically identical trials with inclusion of patients with approximately the same disease duration and JIA categories. Especially the trials included in the network with systemic JIA patients only were highly comparable. Disease duration and presence of systemic JIA were considered to be the most important confounders associated with treatment response, which is supported by the literature.[34, 50] Nevertheless, the included trials were not perfectly identical. Treatment duration varied between trials and is likely to influence the measured outcome. Furthermore, though the similarities predominated, differences between the withdrawal trials included used co-medications and previous treatment with biologic agents of some patients. However, because of the small number of trials (only 1 trial per individual biologic arm) 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 biologic agents in JIA. Taken into account the differences between trials, this is the first study to carefully conclude that the short-term efficacy of etanercept, adalimumab and abatacept seemed similar for poly-articular course JIA and anakinra, canakinumab and tocilizumab similar for systemic JIA. Because of the observed differences between trials, head-to-head trials comparing 2 biologic agents directly are highly needed. 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.

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SUPPLEMENTARY FILES: 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[pt] OR controlled clinical trial[pt] 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 ('anti-rheumatic 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

SUPPLEMENTARY FILES: 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_ai
```

SUPPLEMENTARY FILES: Table A. Description of included studies

	Etanercept (Lovell)	**Infliximab (Ruperto)**	**Adalimumab (Lovell)**	**Abatacept (Ruperto)**	**Tociluzimab (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

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 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

SUPPLEMENTARY FILES: Table A. Description of included studies (continued)

	Etanercept (Lovell)	**Infliximab (Ruperto)**	**Adalimumab (Lovell)**	**Abatacept (Ruperto)**	**Tociluzimab (Yokota)**
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/ m^2/ wk oral or IM	1)Adalimumab 24mg/m^2 (max 40mg) every other week; 2) placebo For those in MTX stratum: stable doses of at least 10mg/m^2/ wk.	1) Abatacept 10mg/kg (max 1000mg); 2) placebo	1) Tocilizumab 8mg/kg every 2 weeks; 2) placebo
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 enrolment (at 10mg/day or 0.2 mg/kg, whichever was less).	IA steroids, methylprednisone 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

Anakinra (Quartier)	**Canakinumab (Ruperto)**	**Tocilizumab (DeBenedetti)**	**Rilonacept (Lovell)**	**Infliximab (Tynjala)**	**Etanercept (Wallace)**
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/m^2/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
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 dosis 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

	Etanercept (Lovell)	Infliximab (Ruperto)	Adalimumab (Lovell)	Abatacept (Ruperto)	Tociluzimab (Yokota)
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% 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]

Anakinra (Quartier)	Canakinumab (Ruperto)	Tocilizumab (DeBenedetti)	Rilonacept (Lovell)	Infliximab (Tynjala)	Etanercept (Wallace)
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)

SUPPLEMENTARY FILES: Table B. Patient population included and reported efficacy

	Etanercept (Lovell)	Infliximab (Ruperto)	Adalimumab (Lovell)	Abatacept (Ruperto)	Tociluzimab (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**

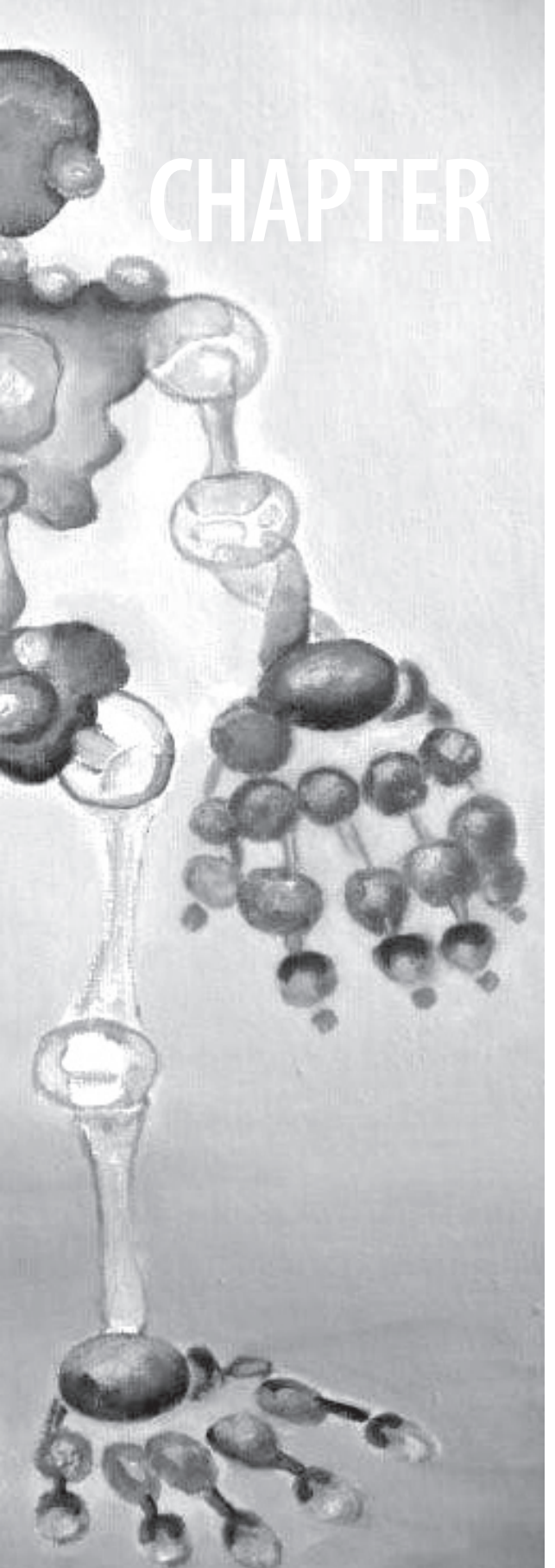
Anakinra (Quartier)	Canakinumab (Ruperto)	Tocilizumab (DeBenedetti)	Rilonacept (Lovell)	ACUTE-JIA (Tynjala)	TREAT (Wallace)
-	-	-	-	-	-
24 (100%)	84 (100%)	112 (100%)	24 (100%)	60 (100%) (efficacy analysis for 59 patients)*	85 (100%)
15 (63%)	?	?	16 (67%)	38 (63%)	72 (85%)
8.5	?	?	12.6	9.6	10.5
3.7	3.4	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
1.55	?	?	1.5	0.76	1.2
50	?	?	?	36	37

	Etanercept (Lovell)	Infliximab (Ruperto)	Adalimumab (Lovell)	Abatacept (Ruperto)	Tociluzimab (Yokota)
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***	-	-	-	-	-
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.

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: 67% PLAC: 8%	DRUG: 84% PLAC: 10%	DRUG: 85% PLAC: 24%	? (numbers unknown)	-	-
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%

** 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



CHAPTER 3

Effectiveness and safety of a first introduced biologic agent in JIA

CHAPTER 3.1

Factors associated with treatment response to etanercept in JIA

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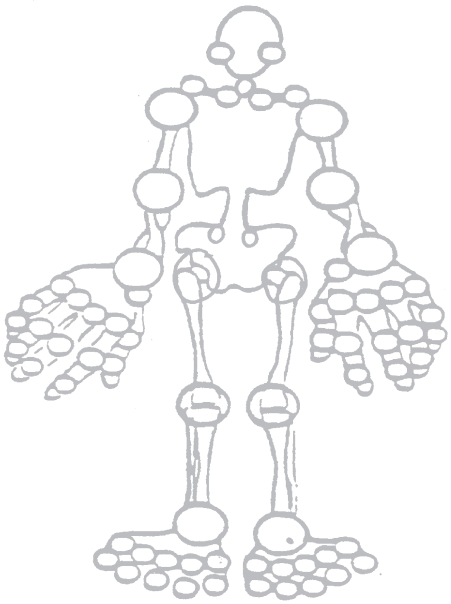

ABSTRACT

Context: Since the introduction of biologic therapies, the pharmacological treatment approach for juvenile idiopathic arthritis (JIA) has changed substantially, with achievement of inactive disease as realistic goal.

Objective: To determine the response to therapy after initiation of etanercept therapy among patients with JIA and to examine the association between baseline factors and response to etanercept treatment.

Design, Setting, and Patients: The Arthritis and Biologics in Children Register (prospective observational study, ongoing since 1999), consists of all Dutch JIA patients who used biologics. All biologic-naive patients who started etanercept before October 2009 were included, with follow up data until January 2011. Among the 262 patients, 185 (71%) were female, 48 (18%) had systemic-onset JIA, and the median age at initiation of etanercept treatment was 12.4 years.

Main outcome measures: Excellent response (inactive disease or discontinuation earlier due to disease remission), intermediate response (more than 50% improvement from baseline, but no inactive disease) and poor response (less than 50% improvement from baseline, or discontinuation earlier due to ineffectiveness or intolerance) evaluated 15 months after initiation of etanercept.

Results: At 15 months following initiation of etanercept treatment, 85 patients (32%) were considered excellent responders, 92 patients (36%) were considered intermediate responders, and 85 patients (32%) were considered poor responders. Compared to achieving an intermediate or poor response, achievement of an excellent response was associated with lower baseline disability score (range 0-3 points, with 0 best score; adjusted OR per point increase, 0.49, 95% CI 0.33-0.74); fewer DMARDs (including methotrexate) used before start etanercept (aOR per DMARD used, 0.64 (95% CI 0.43-0.95), and younger age at onset (aOR per year increase, 0.92, 95% CI 0.84-0.99). Compared to achieving an intermediate or excellent response, achievement of a poor response was associated with systemic JIA (aOR systemic vs non-systemic categories, 2.92 95% CI 1.26-6.80), and female gender (aOR female vs male, 2.16 (95% CI 1.12-4.18). Within the first 15 months of etanercept treatment, 119 patients experienced one or more infections, non-infectious, or serious adverse events, and 61 patients discontinued etanercept treatment, including 4 among those with an excellent response, 0 among those with an intermediate response, and 57 among those with a poor response. In a secondary analysis of longer term follow-up of 262 patients with a median follow-up of

35.6 months after initiation of etanercept, a range of 37-49% of patients reached inactive disease. Mean drug survival was 49.2 (95% CI 46.4-52.0) months for patients that had achieved an excellent response after 15 months, 47.5 (95% CI 44.9-50.1) months for patients that had achieved intermediate response, and 17.4 (95% CI 13.6-21.2) months for patients that had achieved a poor response.

Conclusions: Among patients with JIA who initiated treatment with etanercept, one-third achieved an excellent response, one-third an intermediate response, and one-third a poor response to therapy. Achievement of an excellent response was associated with low baseline disability scores, fewer DMARDs used before etanercept and younger age at onset JIA, and achievement of a poor treatment response with systemic JIA and female gender.

INTRODUCTION

Etanercept, a tumour necrosis factor alpha antagonist, was approved a decade ago by the Food and Drug Administration and European Medicines Agency for the treatment of juvenile idiopathic arthritis (JIA). The efficacy of etanercept for patients with JIA and a poly-articular course has been established in a randomized placebo-controlled withdrawal trial that showed American College of Rheumatology Paediatric (ACRpedi) 30 responses (30% improvement from baseline) in over 70% of the patients.[1] Several observational studies, including the Dutch Arthritis and Biologics in Children (ABC) Register, confirmed the effectiveness of etanercept in daily practice.[2-4] Since the development of biologics, the pharmacological treatment approach of JIA is changing rapidly and synthetic disease-modifying anti-rheumatic agents (DMARDs) are used earlier in the disease course, which seem to provide better long-term outcomes.[5-6] As a result of these treatment successes, a treatment goal of reaching inactive disease now seems realistic. However, inactive disease is still not achieved in a substantial proportion of cases and current approaches need to be optimized even more[2-4]. Although factors associated with methotrexate response have been analyzed, factors associated with the effect of etanercept treatment in JIA are still unknown.[7] The ability to identify patients who are more likely to respond to etanercept treatment would be an important step towards tailored patient-specific treatment and subsequently could improve current treatment approaches.

Therefore, the objectives of this study were to evaluate disease activity after etanercept initiation in daily practice, and to identify baseline characteristics associated with etanercept treatment response in JIA patients.

PATIENTS AND METHODS

Study design and subjects

This study is part of a multicenter prospective observational register; the ABC Register. This Register (founded with the introduction of biologics in 1999), includes all JIA patients in the Netherlands who use or previously used biologic agents.

The study protocol was approved by the Medical Ethics Committee at Erasmus MC Rotterdam and by all participating hospitals. Written informed consent was obtained from parents and from participants above 12 years of age. In the Register (which became web-based in 2008), patient and disease characteristics are collected at baseline, followed by data collection after 3 months of treatment and yearly thereafter.[8] This includes (among others) the variables of the JIA disease activity score (i.e. 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 entering follow-up data at 3 months and yearly, extra data entry times were at the time of any important events including, when biologics were discontinued, type of biologic switched or when there were safety concerns. On average, 6 data entry points per patient were available.
For this study we selected all JIA patients in whom etanercept was initiated as the first biologic treatment and who could have had at least 15 months of follow up. Follow up data until January 2011 were used.

Response to therapy was assessed using the ACRpedi 30, 50, and 70 criteria. For each variable of the JIA core set improvement from baseline has been expressed as a percentage. The definition of an ACRpedi 30, 50, and 70 response states that there should be at least, depending on the score, 30% or 50% or 70% improvement from baseline in three or more variables of the JIA core set, with no more than one variable worsening by more than 30%.[9] 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).[10]

Factors associated with treatment response

Based on literature, we analyzed the following potential baseline factors for treatment response: gender, age at JIA onset, disease duration until start of etanercept, ANA positivity, JIA category (systemic-onset vs. all other categories), number of DMARDs (including methotrexate) used before start of etanercept, and, at initiation of etanercept, physician's global assessment of disease activity, CHAQ score, and ESR. Based on the number of patients in the study, we restricted the number of factors and assumed that the number of active joints with arthritis in the physician's global assessment and the number of joints with limited motion in the CHAQ score reflected each other.

An excellent treatment response was defined as achievement of inactive disease after 15 months (range 12-18 months) of treatment or within this time frame ever discontinuation of etanercept because of disease remission. An intermediate response was defined as achievement of an ACRpedi50 response after 15 months of treatment, but no inactive disease. A poor response to treatment was defined as no achievement of an ACRpedi50 response after 15 months of treatment, or within these 15 months ever discontinuation of etanercept due to ineffectiveness or adverse events (AEs).

Safety analysis

All infectious and non-infectious AEs and all serious adverse events (SAEs) were reported by the physician on a continuous basis. Serious adverse events were defined as life-threatening or fatal events, events resulting in persistent or significant disability, events requiring intervention to prevent permanent impairment or damage, congenital anomalies, or hospitalization or prolongation of existing hospitalization. Flaring of JIA was not considered as an AE but as measurement of treatment response.
We calculated the rate of SAEs, infectious AEs and non-infectious AEs on the basis of the duration of etanercept exposure. We considered recurrent infections as separate AEs. If non-infectious AEs were reported repeatedly within the same patient we counted them only once. Factors to identify patients who experienced AEs within the first 15 months were analyzed. We also analyzed the number of AEs between 3 and 15 months of follow-up in those patients using a combination of etanercept and methotrexate, and in those using monotherapy etanercept.

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 times (13.6% of the JIA core set variables were missing; 4.0% of active and 7.1% of limited joint counts, 7.6% of ESR values, 19.4% of physician's global assessment of disease activity scores, 23.1% of CHAQ scores, 20.6% of global assessment of wellbeing scores were missing; per core set median of 0 (interquartile range; IQR 0-1) variables missing).
Descriptive statistics were reported as absolute frequencies, or as median values with IQR. Depending on the variable tested, the Mann-Whitney U-test and the Pearson chi-square test were used to perform comparisons. A univariable and multivariable logistic regression analysis was performed to identify potential baseline factors associated with achieved treatment response (comparing excellent response vs poor and intermediate response combined and comparing poor response vs intermediate and excellent responses combined). To identify patients who experienced AEs within the first 15 months, a multivariate logistic regression analysis for binary outcome was performed. Results are presented as adjusted odds ratios (aOR; the OR for each covariate was adjusted for the effects of the other covariates) with 95% confidence intervals (CI); p-values were calculated with the Wald's test.

We also conducted secondary analyses of longer-term outcomes. Drug survival was estimated with Kaplan-Meier plots (truncated until at least 10% of the original population was in follow up) and differences between the systemic-onset JIA and all other JIA categories (i.e. non-systemic categories) were defined by the log-rank test. To account for correlations between repeated measurements and missing follow-up times mixed

models for binary response data (GLIMMIX) were used to perform the long-term effectiveness analyses.

All reported p-values were based on 2-sided tests for significance, and p-values <0.05 were considered statistically significant. SPSS version 17.0.1, *R* statistical package 2.12.1, and SAS version 9.2 were used for the analyses.

RESULTS

Patient characteristics and medications

A total of 262 previously biologic-naive JIA patients who started etanercept were included in the analysis. Table 1 presents the patient and disease characteristics of these patients. The total follow-up duration was 881.4 patient-years (of which 683.7 patient-years exposed to etanercept), with a median follow-up time of 35.6 (IQR 17.4-53.6) months per patient.

At etanercept initiation, 37% of patients used concomitant systemic corticosteroids, 89% methotrexate, and 7% other DMARDs. After 15 months of etanercept treatment, systemic corticosteroids were discontinued in 69% of the patients using it at start, methotrexate in 42%, and other DMARDs in 88%. During the first 15 months of treatment, only small numbers of patients started concomitant medication (9 systemic corticosteroids, 2 methotrexate, and 5 other DMARDs).

Response to therapy at 15 months

Of the 262 patients, 85 (32%) were considered excellent responders after 15 months of treatment (81 patients achieved inactive disease after 15 months and 4 patients discontinued etanercept up to that time point because of remission). A total of 85 patients (32%) were considered poor responders (44 patients had discontinued etanercept because of ineffectiveness, 13 because of adverse events, and 28 patients had not reached an ACRpedi50 response after 15 months of treatment). The remaining 92 patients were considered intermediate responders. Table 1 presents the patient and disease characteristics for the excellent, intermediate, and poor responders.

The aORs are shown for association between pre-specified baseline variables and response to therapy in logistic regression analysis, comparing excellent responses vs poor and intermediate (Table 2a) and comparing poor responses vs intermediate and excellent (Table 2b). Compared to achieving an intermediate or poor response, achievement of an excellent response was associated with lower baseline CHAQ scores (aOR per point increase, 0.49, 95% CI 0.33-0.74); low number of DMARDs (including methotrexate) used before introduction of etanercept (aOR per DMARD used, 0.64 (95% CI 0.43-0.95), and younger age at onset (aOR per year increase, 0.92, 95% CI 0.84-0.99). Compared to

TABLE 1. Patient and disease characteristics at baseline

Baseline characteristics	All JIA patients (n=262)	Excellent responders* (n=85)	Intermediate responders* (n=92)	Poor responders* (n=85)
Patient characteristics				
Female, No. (%)	185 (71)	57 (67)	60 (65)	68 (80)
Age at onset JIA, median (IQR), y	6.9 (3.6-11.1)	6.5 (3.3-9.8)	7.0 (3.4-11.3)	9.0 (3.7-12.2)
Age at start etanercept, median (IQR), y	12.4 (9.3-14.9)	12.0 (9.1-15.1)	12.6 (9.0-14.7)	12.5 (9.4-15.5)
Disease duration before start etanercept, median (IQR), y	3.0 (1.5-6.8)	3.6 (1.8-7.8)	3.1 (1.5-6.6)	2.3 (1.2-4.5)
Systemic-onset JIA, No. (%)	46 (18)	11 (13)	15 (16)	20 (24)
Polyarticular JIA RF negative, No. (%)	102 (39)	32 (38)	38 (41)	32 (38)
Polyarticular JIA RF positive, No. (%)	23 (9)	5 (6)	8 (9)	10 (12)
Oligoarticular JIA persistent, No. (%)	5 (2)	4 (5)	1 (1)	0 (0)
Oligoarticular JIA extended, No. (%)	57 (22)	22 (26)	18 (20)	17 (20)
Arthritis psoriatica, No. (%)	17 (6)	6 (7)	7 (8)	4 (5)
Enthesitis-related arthritis, No. (%)	12 (5)	5 (6)	5 (5)	2 (2)
ANA positivity, No. (%)	60 (23)	20 (24)	19 (21)	21 (25)
Ever used medications before start of etanercept				
NSAIDs, No. (%)	257 (98)	83 (98)	92 (100)	82 (96)
Corticosteroids systemic, No. (%)	133 (51)	37 (44)	49 (53)	47 (55)
Corticosteroids intra-articular, No. (%)	66 (25)	26 (31)	25 (27)	15 (18)
Methotrexate, No. (%)	227 (87)	72 (85)	78 (85)	77 (91)
Other DMARDs, No. (%)	115 (44)	36 (42)	47 (51)	32 (38)
Number of DMARDs (incl. methotrexate) used, median (IQR)	1 (1-1)	1 (1-2)	1.5 (1-2)	1 (1-2)
Concomitant medication at start of etanercept				
NSAIDs, No. (%)	217 (83)	67 (79)	84 (91)	66 (78)
Corticosteroids systemic, No. (%)	96 (37)	25 (29)	37 (40)	34 (40)
Corticosteroids intra-articular, No. (%)	8 (3)	4 (5)	4 (4)	0 (0)
Methotrexate, No. (%)	234 (89)	75 (88)	86 (93)	73 (86)
Other DMARDs, No. (%)	19 (7)	3 (4)	11 (12)	5 (6)
Disease characteristics at start of etanercept				
VAS disease activity by physician, median (IQR), mm	63 (45-75)	57 (40-73)	67 (56-78)	61 (43-72)
Number of active joints, median (IQR)	10 (6-18)	8 (5-15)	10 (6-22)	12 (8-18)
Number of limited joints, median (IQR)	7 (4-13)	6 (2-12)	10 (4-15)	6 (4-13)
CHAQ score (0-3), median (IQR)	1.5 (1.0-2.1)	1.1 (1.1-2.0)	1.8 (1.2-2.3)	1.8 (1.1-2.0)
VAS pain by patient/parent, median (IQR), mm	57 (29-76)	52 (17-77)	54 (31-72)	56 (30-75)
VAS wellbeing by patient/parent, median (IQR), mm	53 (29-75)	50 (21-77)	54 (30-75)	60 (35-75)
Erythrocyte Sedimentation Rate, median (IQR), mm/hour	21 (9-37)	19 (10-33)	29 (12-44)	15 (8-35)

*Measured after 15 (range 12-18) months of treatment
[JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; ANA=Anti-Nuclear-Antibody; DMARDs=disease-modifying anti-rheumatic agents; VAS=visual analogue scale; CHAQ=child health assessment questionnaire]

TABLE 2A. Factors associated with excellent response to etanercept

Variable	Absolute risk		Univariable			Multivariable		
	% excellent responders N=85	% intermediate/ poor responders N=177	OR	95% CI	p-value	aOR	95% CI	p-value
Female (vs. male)	67%	72%	0.78	(0.45-1.36)	0.38	0.85	(0.45-1.59)	0.61
Systemic-onset JIA (vs. non-systemic subtypes)	13%	20%	0.60	(0.29-1.26)	0.18	0.49	(0.20-1.18)	0.11
ANA positivity (vs. negativity)	24%	23%	1.05	(0.57-1.95)	0.87	0.73	(0.37-1.46)	0.38
Age of onset JIA (per year)	6%	7%	0.94	(0.89-1.00)	0.06	0.92	(0.84-0.99)	0.03
Disease duration before start etanercept (per year)	10%	11%	1.08	(1.01-1.15)	0.04	1.05	(0.96-1.15)	0.26
Number of DMARDs (incl. methotrexate) used before start etanercept (per DMARD used)	17%	18%	0.90	(0.64-1.25)	0.52	0.64	(0.43-0.95)	0.03
VAS disease activity by physician at start etanercept (per 10 points increase)	10%	11%	0.86	(0. 67-0.97)	0.02	0.89	(0.77-1.02)	0.10
CHAQ score at start etanercept (per 1 point increase)	33%	42%	0.49	(0.34-0.71)	<0.001	0.49	(0.33-0.74)	0.001
ESR at start etanercept (per 1 unit (mm/h) increase)	3%	3%	0.84	(0.50-1.41)	0.51	1.03	(0.57-1.85)	0.92

TABLE 2B. Factors associated with poor response to etanercept comparing with an intermediate and excellent response combined

Variable	Absolute risk		Univariable			Multivariable		
	Poor N=85	Intermediate/ excellent N=177	OR	95% CI	p-value	aOR	95% CI	p-value
Female (vs. male)	80%	66%	2.05	(1.11-3.80)	0.02	2.16	(1.12-4.18)	0.02
Systemic-onset JIA (vs. non-systemic subtypes)	24%	15%	1.79	(0.93-3.43)	0.08	2.92	(1.26-6.80)	0.01
ANA positivity (vs. negativity)	25%	22%	1.16	(0.63-2.13)	0.63	1.29	(0.66-2.52)	0.47
Age of onset JIA (per year)	7%	7%	1.07	(1.01-1.14)	0.02	1.08	(0.99-1.16)	0.07
Disease duration before start etanercept (per year)	11%	10%	0.92	(0.85-1.00)	0.04	0.95	(0.87-1.05)	0.31
Number of DMARDs (incl. methotrexate) used before start etanercept	19%	17%	0.98	(0.70-1.36)	0.89	1.21	(0.83-1.76)	0.33
VAS disease activity by physician at start etanercept (per 10 points increase)	11%	11%	0.96	(0.85-1.09)	0.14	0.95	(0.83-1.09)	0.53
CHAQ score at start etanercept (per 1 point increase)	42%	37%	1.31	(0.93-1.85)	0.13	1.47	(0.98-2.20)	0.07
ESR at start etanercept (per 1 unit (mm/h) increase)	3%	3%	1.00	(1.00-1.00)	0.77	0.99	(0.98-1.00)	0.21

[aOR=adjusted odds ratio; CI=confidence interval; REF=reference category; JIA=juvenile idiopathic arthritis; ANA=Anti-Nuclear-Antibody; DMARDs=disease-modifying anti-rheumatic agents; VAS=visual analogue scale; CHAQ=child health assessment questionnaire; ESR=erythrocyte sedimentation rate]

* Interpretation of absolute risks:
For dichotomous variables: of the poor responders 80% was female, while of the intermediate and excellent responders combined 66% was female.
For continuous variables: 33% increase in excellent responders was seen for each point increase of CHAQ score, while 42% increase in intermediate and poor responders combined was seen for each point increase of CHAQ score.

achieving an intermediate or excellent response, achievement of a poor response was associated with systemic JIA (aOR systemic JIA vs. non-systemic categories, 2.92 95% CI 1.26-6.80), and female gender (aOR female vs. male, 2.16 (95% CI 1.12-4.18). Treatment response did not appear to be associated with ANA positivity, disease duration, physician's global assessment of disease activity or ESR at baseline.

Adverse events during first 15 months

Within the first 15 months of treatment, 119 patients experienced one or more AE (infectious, non-infectious or serious; including 37 patients among those with an excellent response, 36 among those with an intermediate response, and 46 among those with a poor response) and 53 patients reported at least one infectious AE or an infectious SAE. These patients could not be identified beforehand with regard to ANA status, JIA category, disease duration and concomitant drugs used (Table 3). Of the 245 patients with 15 months of follow up, 104 patients used concomitant methotrexate between 3 and 15 months of follow up and 84 patients used monotherapy etanercept. Between 3 and 15 months of treatment these patients experienced 0.48 AEs and 0.24 infectious AEs/ patient-year of combination (etanercept and methotrexate) therapy, and 0.39 AEs and 0.13 infectious AEs/ patient-year of etanercept mono-therapy (infectious AEs: p=0.058, Pearson Chi-square).

Drug discontinuation during first 15 months

During the first 15 months of treatment, 61 patients (23% of all 262 patients) discontinued etanercept. The reason for discontinuation was in 44 patients because of ineffectiveness of treatment and in 13 patients because of adverse events. Four patients discontinued etanercept because of disease remission after a median of 14.1 (IQR 12.8-14.5) months, of whom 3 patients relapsed and restarted treatment after a median of 3.8 months.

Longer term follow-up

Table 4 shows the response to treatment following introduction of etanercept over a 7-year follow-up period on the basis of intention-to-treat (i.e. regardless of discontinuations of etanercept or switching to other treatments). By 51 months of treatment, 94% (95% CI 89%-98%) of the patients reached an ACRpedi50 response, 76% (95% CI 65%-87%) an ACRpedi70 response and 40% (95% CI 26%-54%) inactive disease.

The cumulative drug survival of etanercept for different JIA categories is shown in Figure 1. The median drug survival (i.e. median duration from start until first discontinuation due to ineffectiveness or AEs) was lower for systemic-onset JIA (29.0 months, 95% CI 11.0-47.0) than for the non-systemic categories (76.8 months, 95% CI 45.7-108.0) (log-rank test p=0.03).

TABLE 3. Factors associated with the occurrence of adverse events within the first 15 months after etanercept initiation

Characteristic	Coding	AE rates		Multivariable logistic regression model			
		All AEs	Infectious AEs	All AEs		Infectious AEs	
		No. events/ patient (mean /median)	No. events/ patient (mean /median)	aOR (95% CI)	p-value	aOR (95% CI)	p-value
ANA status	Positive	0.85 / 1.00	0.23 / 0.00	1.39 (0.77-2.53)	0.28	0.83 (0.39-1.78)	0.64
	Negative	0.67 / 0.00	0.24 / 0.00	1.0 (ref)		1.0 (ref)	
JIA category	Systemic-onset JIA	0.70 / 0.00	0.30 / 0.00	0.77 (0.37-1.58)	0.47	1.42 (0.59-3.44)	0.44
	Non-systemic categories	0.72 / 0.00	0.23 / 0.00	1.0 (ref)		1.0 (ref)	
Concomitant corticosteroid use at start of etanercept	Yes	0.79 / 0.00	0.22 / 0.00	1.03 (0.59-1.81)	0.92	0.59 (0.28-1.24)	0.17
	No	0.67 / 0.00	0.25 / 0.00	1.0 (ref)		1.0 (ref)	
Concomitant methotrexate use at start of etanercept	Yes	0.69 / 0.00	0.24 / 0.00	0.69 (0.31-1.52)	0.35	0.71 (0.28-1.79)	0.46
	No	0.93 / 1.00	0.29 / 0.00	1.0 (ref)		1.0 (ref)	
Disease duration before start of etanercept	Per year increase	-	-	0.96 (0.89-1.03)	0.21	0.97 (0.89-1.06)	0.47

[AEs=adverse events; OR=odds ratio; CI=confidence interval; ANA=Anti-Nuclear-Antibody; JIA=juvenile idiopathic arthritis]

TABLE 4. Improvement from baseline after etanercept initiation; long term follow-up

Duration after etanercept initiation	Response groups as defined at 15 months of followup			Mixed model			
	Poor response % of patients	Intermediate response % of patients	Excellent response % of patients	ACRpedi30 % (95% CI)	ACRpedi50 % (95% CI)	ACRpedi70 % (95% CI)	Inactive Disease % (95% CI)
3 months (N=262)	32	35	32	89 (84-94)	72 (64-80)	48 (39-56)	11 (6-16)
15 months (N=245)	28	38	35	93 (90-97)	87 (82-93)	70 (62-77)	32 (24-40)
27 months (N=177)	28	38	34	93 (88-97)	88 (82 (93)	70 (61-79)	37 (27-47)
39 months (N=130)	22	46	32	88 (81-95)	85 (77-92)	74 (64-83)	37 (26-48)
51 months (N=83)	17	53	30	95 (91-99)	94 (89-98)	76 (65-87)	40 (26-54)
63 months (N=60)	22	52	27	92 (85-100)	89 (80-97)	80 (68-92)	41 (24-58)
75 months (N=30)	23	53	23	90 (79-101)	87 (74-100)	66 (44-88)	49 (24-73)
87 months (N=17)	41	53	6	82 (64-101)	70 (43-97)	63 (34-93)	45 (13-77)

Table 4 is on the basis of an intention-to-treat analysis (i.e. response since introduction of etanercept; discontinuations of etanercept or switching to other treatments not taken into account) with the use of mixed models to account for correlations between repeated measurements and to account for missing follow-up moments (GLIMMIX). The percentages of patients who reached the criteria for ACRpedi30/50/70 responses and inactive disease at the different follow-up moments since start of etanercept are given. The percentages of patients that reached the criteria for ACRpedi30/50/70 responses and inactive disease are not mutually exclusive; patients that achieve inactive disease are also included in the ACRpedi30/50/70 responses, patients that achieve an ACRpedi70 response are also included in the ACRpedi30 and 50 responses, etc.

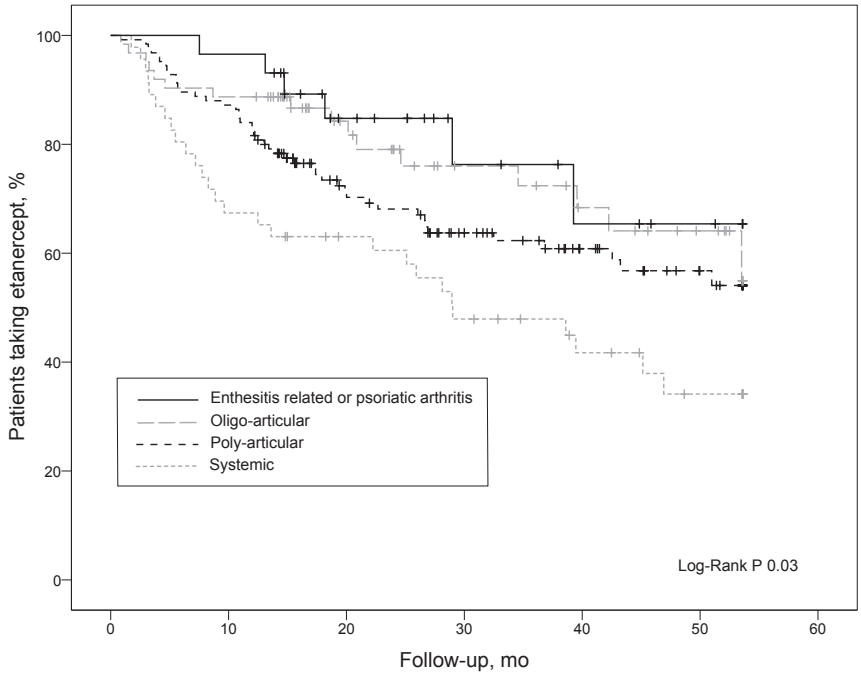

FIGURE 1. Adherence to treatment after introduction of etanercept
The event is defined as the first time a patient discontinued use of etanercept due to inefficacy, adverse events, or nonadherence. Censoring is defined as the time a patient discontinued because of remission or end of follow-up (to adult care), which is represented by the small vertical lines on the curves. Restart of etanercept is not taken into account. The number at risk are patients with systemic onset of juvenile idiopathic arthritis (JIA), polyarticular JIA (rheumatoid factor positive and negative), oligoarticular JIA (persistent and extended), who were still receiving etanercept at the different time points is shown. For systemic-onset JIA the median adherence to etanercept was 29.0 months (95% CI, 11.0-47.0). For nonsystemic JIA categories, the median adherence was 76.8 months (95% CI, 45.7-108.0). Log-rank test compares the drug survival difference between systemic-onset and nonsystemic categories (P log-rank 0.03).

Table accompanying Figure 1:

Follow-up (months)	0	10	20	30	40	50
N systemic-onset JIA	46	31	25	19	13	8
N poly articular JIA (RF positive and negative)	125	107	66	48	33	21
N oligo articular JIA (extended or persistent)	62	54	32	20	15	10
N enthesitis related or psoriatic arthritis	29	28	17	9	6	4
N total	262	220	140	96	67	43

During follow-up, 142 patients (54% of all 262 patients) discontinued etanercept. The reason for discontinuation in 78 patients was ineffectiveness of treatment; these patients discontinued etanercept after a median treatment duration of 14.2 (IQR 5.7-27.2) months; however, 12 patients restarted etanercept after 4.4 (IQR 2.3-6.5) years. In 25 patients etanercept was discontinued because of AEs after a median duration of 8.3 (IQR 2.5-17.6) months; of these 25 patients, 6 temporarily discontinued etanercept.
Withdrawal of etanercept because of disease remission (according to the judgment of the treating physician) occurred in 39 patients after a median of 36.9 (IQR 24.0-48.1) months. Of the patients who discontinued etanercept because of remission (median follow up duration after etanercept discontinuation for these patients was 13.4 (IQR 5.3-24.7) months), 15 flared and restarted etanercept treatment. These 15 patients had an initial shorter course with etanercept (28.6 months, IQR 18.6-41.3) than patients who did not flare (45.0 months, IQR 28.0-55.6; p=0.03). At the time of treatment discontinuation due to remission, 10 of 39 patients (26%) still used concomitantly methotrexate and 6 of 39 patients (15%) NSAIDs, no patients used concomitantly systemic corticosteroids.

Safety analysis

During etanercept treatment, a total of 31 SAEs, 99 infectious AEs, and 179 non-infectious AEs were reported. This resulted in 0.05 SAEs, 0.14 infectious AEs and 0.26 non-infectious AEs per patient-year of etanercept exposure. (All reported SAEs and AEs are summarized in eTable 1 and 2)

eTABLE 1 Serious adverse events

Serious adverse events during etanercept use (n=31)	**Number**
Development of de novo auto-immune diseases	
M. Crohn	2
Colitis Ulcerosa	2
Sarcoidosis	2
Psoriatic skin lesions	3
Severe infections requiring hospitalization	
Uro-sepsis	2
Gastro-intestinal infections	2
Severe ear-nose-throat infections	2
Skin infection (cellulitis)	1
Neurological symptoms	
Multiple sclerosis-like symptoms	1
Multiple epileptic attacks	1
Epileptic-like attack	1
Syncope of unknown origin	1
Other	
Fibro-adenoma left breast	1
Lung emboli	1
Hemoptoesis	1
Anorexia Nervosa	1
Weight loss of unknown cause (-13kg)	1
Chest pain of unknown cause	1
Combination of weight loss (-3kg) and chest pain	1
Ovarian cyst torsion requiring surgical reposition	1
Urine-incontinency requiring surgical intervention	1
Fracture wrist and hyperventilation	1
Pregnancy	1
Malignancies	*none*
Serious adverse events in patients previously treated with etanercept (n=7)	
Death of unknown cause*	2
Severe infections requiring hospitalization	4
Chest pain and breathing difficulties of unknown cause	1

Hospitalization occurred 22 times: median duration 9 (IQR 2- 12) days.
* One patient died while using anakinra, 4.8 years after discontinuation of etanercept. Another patient died 0.7 years after discontinuation of etanercept. The cause of death is in both cases unknown; in one a fulminate sepsis or exacerbation of the disease was suspected, and in the other patient multiple lung emboli or lung infiltrates in a TBC-positive patient after removal of a Hickman line.[e-ref]

[e-ref] Armbrust W, Kamphuis SS, Wolfs TW, et al. Tuberculosis in a nine-year-old girl treated with infliximab for systemic juvenile idiopathic arthritis. Rheumatology (Oxford) 2004;43:527-9.

eTABLE 2 Non-serious adverse events

Adverse events during etanercept use	Number
Infectious (n=99)	
Fever of unknown origin	15
Skin infections	19
Ear-nose-throat infections	16
Upper respiratory tract infections	13
Pneumonia	1
Gastro-intestinal infections	10
Infections of the eye (no uveitis)	2
Urinary tract infections	4
Fungal infections	4
Herpes simplex infections	7
Epstein Barr infections	3
Varicella-Zoster infections	4
Hepatitis A infection	1
Non-infectious (n=179)	
Injection-site reactions	26
Allergic reaction, rash, skin lesions	23
Gastro-intestinal complaints (abdominal pain, nausea or vomiting)	24
Headache	17
Fatigue	15
Dizziness or fainting	7
Malaise	1
Pain in ear, nose or throat (without infection)	5
Coughing or urge to cough	3
Chest pain, shortness of breath, or hyperventilation	5
Hypertension	2
Tendo-myogenic pain	8
Lymphadenopathy	3
Alopecia	4
Hematomas or nose bleedings	8
Anemia	2
Neuropathy	2
Concentration difficulties, memory problems or behavioral problems	4
Mood disorders	4
Discrepancy between pain severity and objective arthritis	1
Sleeping difficulties	6
Urinary complaints (hesitation or pain, without infection)	2
Adipositas	2
Osteoporosis	1
Delayed puberty	1
Irregular menstruation	1
Bone fracture	2

DISCUSSION

Comparing excellent with intermediate and poor response combined and poor response with intermediate and excellent response combined allowed us to analyze factors associated with etanercept treatment response after 15 months of treatment. An excellent response, reached in already one-third of the patients after 15 months of etanercept treatment, was associated with lower disability scores and fewer DMARDs used before the introduction of etanercept. In adult patients with rheumatoid arthritis, many studies showed an association between lower disability scores and fewer DMARDs used before etanercept and good responses to etanercept.[11-16] The PRINTO group analyzed factors associated with poor response to methotrexate treatment in JIA patients and found, among others, an association with longer disease duration and higher CHAQ scores[7]. These results seem to indicate that longer disease duration with more disability is associated with a worse response, indicating a window of opportunity. The observation that the achievement of better outcomes was related with earlier treatment introduction has been reported previously for methotrexate and sulfasalazine.[5-6]

In this study, the strongest association with a poor response to etanercept was the systemic-onset JIA. Systemic-onset JIA patients had 3-times higher odds to achieve a poor treatment outcome compared with the non-systemic JIA categories and more systemic-onset JIA patients discontinued etanercept over time. This negative relation with the systemic-onset JIA was expected, as systemic-onset JIA is the most therapy-resistant JIA category. However, 11 out of the 46 (24%) systemic-onset JIA patients included were excellent responders after 15 months of treatment. Surprisingly, the PRINTO group found no association between poor methotrexate response and systemic-onset JIA, although 14% of their JIA patients had the systemic-onset JIA.[7] Our results for less favourable treatment response are consistent with two recent studies, both reporting on the association between discontinuation of etanercept due to ineffectiveness and systemic-onset JIA.[17-18]

Results of observational studies with anakinra, an IL-1-receptor antagonist, are promising.[19-21] The ACR recommends anakinra for systemic-onset JIA with active systemic features, and equally etanercept or anakinra for systemic-onset JIA with active arthritis.[22] Also our results indicate that some systemic JIA patients do benefit from etanercept treatment. More observational data and comparisons of treatment strategies targeting different cytokines for systemic-onset JIA are needed.

A poor etanercept treatment response was also associated with female gender and an excellent response with younger age at onset. It is known that the female gender is associated with worse response for both JIA patients and rheumatoid arthritis patients. This prognostic factor is probably related to the different JIA categories which also reflect different prognosis.

We also found a possible association between concomitant methotrexate use within the first 15 months of treatment and more infectious AEs; however, this was borderline significant. At baseline, we were unable to identify patients who were prone to develop AEs within the first 15 months of treatment. Therefore, the treating physician should always be alert for the development of possible AEs.

In a secondary analysis of longer term follow-up, this national observational cohort study shows that, 4 to 7 years after initiation of etanercept, in daily practice, a range of 37-49% of the patients had achieved inactive disease. While, of these patients with years of follow-up after etanercept initiation, less than on-third was considered an excellent responder after 15 months. Besides optimization of the different treatment approaches, we also need to optimize the duration of etanercept treatment. While a range of 37-49% of the patients reached inactive disease, only 39 of the 262 patients (15%) tried to discontinue etanercept. Of these 39 patients, 15 relapsed and needed to restart etanercept. This relapse rate after discontinuation (38%) is relatively low compared to studies that reported relapse rates of 47-80%.[18, 23-24] The optimal duration of inactive disease after which withdrawal of etanercept can be considered is not yet determined.
In the present patient cohort, etanercept was well tolerated. The safety profiles (0.05 SAEs/patient-year) are comparable with the open-label extension trial data (0.12 SAEs/patient-year), and with the German JIA register (0.02 SAEs/patient-year).[2-3] Safety of etanercept and other biologic agents remains an important topic. Until now, no malignancies have been reported in our Register which currently covers a total of 881.4 patient-years of follow-up since introduction of etanercept.

The main strength of the ABC Register is that, since the introduction of etanercept in 1999, all JIA patients who initiated etanercept in the Netherlands are included and no selection bias occurred. However, because of the observational study design, reflecting a real-life setting, the choice of treatment is subject to the knowledge of the treating physicians and differences in approach are known to exist. Furthermore, treatment strategies have changed over recent years. Since our Register covers more than a decade of treatment with etanercept, our study population is also likely to have changed over these years. This study design that requires physicians to record all patients for many years during daily practice increased the risk for missing values. In total 13.6% of the variables of the JIA core set were missing with a median of 0 per core set. Furthermore detailed information on the used concomitant medications in the period between the yearly follow up moments is lacking.
A major limitation of this study is the lack of a control group. In fact none of the above-mentioned studies analyzing baseline factors associated with treatment response (including this study) included a control group. It remains unknown whether patients with

a poor response to etanercept would have responded better to other treatment options. Therefore, our findings (and those of previous studies) mainly reflect overall prognostic factors than predictive factors for etanercept treatment in particular. Head-to-head trials comparing different biologic agents are still lacking for JIA; these are urgently needed, as are randomized controlled trials for different treatment strategies. Furthermore, more research on immunological and genetic parameters is needed to improve treatment prediction and tailored patient care.

In conclusion, 15 months after initiation of etanercept, one-third of the JIA patients achieved an excellent response, one-third an intermediate, and one-third a poor response. An excellent treatment response was associated with low baseline disability scores, low number of DMARDs used before etanercept introduction and younger age at onset JIA, while a poor response was associated with systemic JIA and female gender.

AUTHOR REPLY

Dr Pang and colleagues bring up the importance of the differences in etiology and pathogenesis between systemic JIA compared with other JIA categories. As more insight into the pathogenesis of systemic JIA has been gained, systemic JIA has been considered by many as a different disease entity because of its clinical features and the involvement of different cytokines, such as interleukin 1 (IL-1), IL-6, and IL-18, in addition to tumor necrosis factor (TNF). While newer biological agents targeting the IL-1 and IL-6 cytokines seem important for systemic JIA, since 1999 many patients with systemic JIA have been treated successfully with etanercept, a TNF antagonist, in daily clinical care.[2]

Because systemic JIA is the most distinct category of JIA, it is important to analyze it (versus non-systemic JIA) as a factor of interest associated with etanercept treatment response. In our study, systemic JIA was found to be the strongest factor associated with a poor treatment response. With systemic JIA added as a confounder in the multivariable analysis, an excellent response was associated with younger age at onset, lower number of synthetic disease-modifying anti-rheumatic drugs used before introduction of etanercept, and lower disability scores at baseline. In addition, in a stratified analysis with exclusion of the patients with systemic JIA, the factors associated with excellent response remained.

We agree that it would be interesting to also analyze differences in response within the systemic JIA population. While systemic JIA is distinguished from other JIA categories, differences exist within the category, with some patients with systemic JIA having prominent systemic features and others having a disease course with a destructive, invalidating polyarthritis.[25] These differences within the systemic JIA category are

reflected in our results; although systemic JIA was in general associated with a poor response, 24% of patients with systemic JIA achieved an excellent response. The American College of Rheumatology recommendations also distinguish patients with systemic JIA and presence of systemic features, for whom anakinra (IL-1 blocker) is the first choice for treatment, from patients with systemic JIA and active arthritis, for whom either anakinra or a TNF antagonist is suggested.[22]

To understand the heterogeneity of the disease, analysis of prognostic and predictive factors should eventually go beyond the JIA categories. These categories have been defined with the aim of identifying homogeneous disease groups and are considered a work in progress.[26] While some categories do seem to represent well-characterized groups of patients, other categories seem to include more heterogeneous groups. Discussion is ongoing to identify more homogeneous groups, and new insights into the understanding of the heterogeneity of the disease may lead to a change in the classification of JIA.[27] It is possible that factors associated with etanercept treatment response underlie a specific etiological or pathogenic pathway. However, these pathways are still unknown. In conclusion, a conscientious description of all patients with JIA who are considered for treatment with etanercept is important and could contribute to the development of patient-specific treatment approaches.

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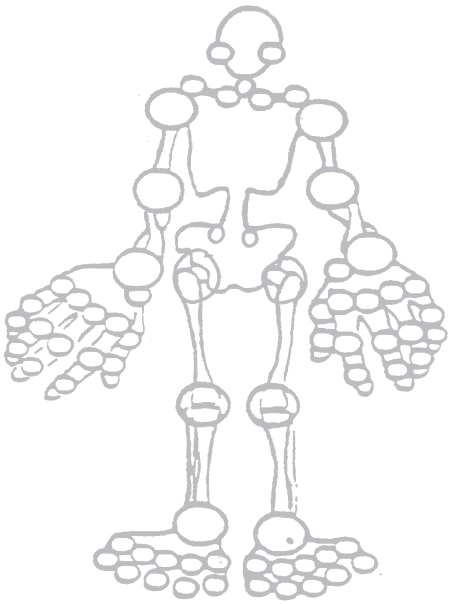
CHAPTER 3.2

TNF-alpha blocking agents in juvenile psoriatic arthritis: are they effective?



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ABSTRACT

Objectives: To evaluate the effectiveness of TNF-blockers in juvenile psoriatic arthritis (JPsA).

Methods: Prospective ongoing multicentre, observational study of all Dutch juvenile idiopathic arthritis (JIA)-patients using biologics. Response of arthritis was assessed by the ACR paediatric response criteria and Wallace inactive disease criteria. Response of psoriatic skin lesions was scored by 5-point scale.

Results: Eighteen JPsA-patients (72% female, median age onset 11.1 (range 3.3-14.6) years, 50% psoriatic skin lesions, 39% nail pitting, 22% dactylitis) were studied. The median follow-up time since start anti-TNF-alpha 26 (range 3-62) months. Seventeen patients started etanercept, one adalimumab. After 3 months of treatment 83% of the patients achieved an ACRpedi30 response, increasing to 100% after 15 months. Inactive disease was reached in 67% after 39 months. There was no discontinuation because of inefficacy. Six patients discontinued treatment after a good clinical response. However, 5 flared and restarted treatment, all with a good response. During treatment 4 patients (2 JPsA and 2 JIA-patients with other subtypes) developed *de novo* psoriasis. In 4 of the 9 patients the pre-existing psoriatic skin lesions improved.

Conclusion: Anti-TNF-alpha therapy in JPsA seems effective in treating arthritis. However, in most patients the arthritis flared after treatment discontinuation, emphasizing the need to investigate optimal therapy duration. The psoriatic skin lesions did not respond well and 4 patients developed *de novo* psoriasis.

INTRODUCTION

Juvenile psoriatic arthritis (JPsA), a subgroup of juvenile idiopathic arthritis (JIA), is defined by the International Association of Rheumatology (ILAR) as arthritis with a typical psoriatic rash, or when this rash is absent with at least two of the following: dactylitis, nail pitting or onycholysis, or psoriasis in a first-degree relative.[1] In adults the psoriatic rash appears to precede the onset of arthritis, but in children the occurrence of arthritis or psoriasis as first symptom seems to be divided evenly.[2] It remains debatable whether this subtype (accounting for 2-11% of JIA patients) represents a clearly defined entity.[3]
Tumour necrosis factor (TNF)-blockers have led to dramatic improvements in JIA-patients with a poly-articular course not responding to the maximum (tolerated) dose of methotrexate (MTX).[4-5] However, no studies have explored JPsA only. In adult-onset PsA, anti-TNF-alpha agents are highly effective and safe.[6-7] As well as the beneficial effects on joints, they are also effective in paediatric psoriatic skin lesions.[8] In contrast, there are reports on induction or exacerbation of psoriasis during anti-TNF-alpha therapy, which seems contradictory since these agents are successful in the treatment of psoriasis.[9] In children only two cases of new-onset psoriatic skin lesions during anti-TNF-alpha therapy have been reported.[10-11]
The present study evaluates the effectiveness of TNF-blocking agents in JPsA-patients on both arthritis and psoriatic skin lesions.

METHODS

This study is part of the the Arthritis and Biologics in Children (ABC)-project, a since 1999 ongoing prospective multicentre, observational study that includes all Dutch JIA-patients using biologics.[5, 12] In the register, patient and disease characteristics are collected at baseline. Data on the JIA core set (physician's global assessment of disease activity by visual analogue scale (VAS) (range 0-100 mm, 0 best score), Childhood Health Assessment Questionnaire (range 0-3, 0 best score) by patients/parents, including global assessment of well-being by VAS, number of active and limited joints and erythrocyte sedimentation rate (ESR)) are retrieved at start, 3, 15 months, and yearly thereafter.
From the patients included in the register until 2010 we selected JPsA patients and JIA patients with subtypes other than JPsA that developed psoriatic skin lesions. Additional data on the diagnostic ILAR criteria for JPsA were collected retrospectively (i.e. presence and type of psoriatic skin lesions, dactylitis, nail pitting or onycholysis, and psoriasis in a first-degree relative).[1]
The response of arthritis was assessed using the ACR paediatric 30, 50 and 70 criteria (ACRpedi30/50/70), defined as at least 30% (50% and 70%, respectively) improvement

from baseline in three or more variables of the JIA core set with no more than one variable worsening by >30%.[13] Inactive disease was defined as: no active arthritis, no uveitis, normal ESR (values under 16 mm/h), and physician's global assessment indicating no disease activity (defined as a score below 10 mm).[14] Responses in JPsA patients were compared to results of the first 146 JIA patients from our register.[5] Response of psoriatic skin lesions was scored from the patients' records using a 5-point scale: markedly improved, improved, no change, worse, and markedly worse.

RESULTS

In total 18 JPsA patients were included. Table 1 shows patient and disease characteristics. Most JPsA patients (94%) were initially treated with etanercept. One patient switched from etanercept to adalimumab because of a severe course of uveitis, but switched back to etanercept after 6 weeks due to a relapse of arthritis. No other patients switched between TNF-blockers or to other biologics.

Psoriatic skin lesions were present in 9 patients (50%): in 4 patients the arthritis preceded the psoriatic skin lesions with 5 (range 2-10) months interval, and 5 patients had psoriatic skin lesions 15 (range 8-62) months before onset arthritis. Two JPsA patients (with arthritis, dactylitis and nail pitting) developed psoriatic skin lesions after introduction of etanercept. These *de novo* psoriatic skin lesions were confirmed by a dermatologist (1 plaque psoriasis and 1 guttate psoriasis). No relation with discontinuation of MTX was found. Table 2 shows the physician-reported response of psoriatic skin lesions to TNF-blockers.
De novo plaque psoriasis during etanercept treatment also occurred in one patient diagnosed as rheumatoid factor negative poly-articular JIA, and one patient as rheumatoid factor positive poly-articular JIA.

Figure 1 presents data on ACRpedi30/50/70 improvement and inactive disease during a follow-up period of 39 months in JPsA patients compared to JIA subtypes. In these first 146 JIA patients no differences in responses were seen between poly-articular rheumatoid factor positive, poly-articular rheumatoid factor negative and oligo-articular subtypes.[5] At 3 months of treatment, 15 of the 18 JPsA patients achieved an ACRpedi30 response, which increased to 100% in the patients that reached 15 months of treatment. Inactive disease was seen in 5 out of 9 JPsA patients with 27 months of follow-up, and 4 out of 6 patients with 39 months of follow-up.
During follow-up MTX was discontinued in 10 patients (59% with concomitant MTX at start) and systemic glucocorticoids and other disease-modifying anti-rheumatic drugs

TABLE 1. Patient and disease characteristics

Characteristics	JPsA (n=18)	All JIA* (n=146)	All non-systemic JIA* (n=107)
Demographic characteristics			
Female (%)	13 (72)	101 (69)	82 (77)
Age onset arthritis (years) (median, range)	11.1 (3.3 -14.6)	11.2 (3.3 -18.6)	12.5 (3.3 -18.6)
Age onset psoriatic skin lesions (years) (median, range)	12.2 (2.8 -15.2)	-	-
Median disease duration before start anti-TNF-α (months) (median, range)	24 (2 -55)	49 (1 -190)	53 (4 -190)
Median follow-up duration since start anti-TNF-α (months) (median, range)	26 (3 -62)	30 (1 -88)	25 (1-83)
Disease characteristics			
≤ 4 active joints at start anti-TNF-α (%)	3 (17)	6 (4)	4 (4)
> 5 active joints at start anti-TNF-α (%)	15 (83)	140 (96)	103 (96)
Psoriatic skin lesions (%)	9 (50)	-	-
Plaque psoriasis	6	-	-
Guttate psoriasis	2	-	-
Inverse psoriasis	1	-	-
Dactylitis (%)	4 (22)	-	-
Nail pitting or onycholysis (%)	7 (39)	-	-
Relative with psoriatic skin lesions (%)	13 (72)	-	-
First-degree	10	-	-
Anti-TNF-α agent			
Etanercept (%)	17 (94)	146 (100)	107 (100)
Adalimumab (%)	1 (6)	-	-
Medication history before start of anti-TNF-α			
Systemic glucocorticoids (%)	7 (39)	90 (62)	52 (49)
Intra-articular glucocorticoids (%)	6 (33)	60 (41)	44 (41)
MTX	17 (94)	146 (100)	107 (100)
Other DMARDs (%)	11 (61)	74 (51)	67 (63)
Concomitant medications at start of anti-TNF-α			
Systemic glucocorticoids (%)	4 (22)	67 (46)	34 (32)
MTX	15 (83)	113 (77)	81 (76)
Other DMARDs (%)	3 (17)	13 (9)	12 (12)

Range is presented as minimum – maximum

*Characteristics of the first 146 JIA patients (107 non-systemic JIA patients) as published from our register. [5]

[JIA = Juvenile Idiopathic Arthritis; TNF = Tumor Necrosis Factor; DMARDs = Disease Modifying Anti-Rheumatic Drugs.]

TABLE 2. Physician-reported response of psoriatic skin lesions to TNF-blockers in JPsA (n=11)

Response	n (%)
Markedly improved	3 (27)
Improved	1 (9)
No change	1 (9)
Worse	1 (9)
Markedly worse	1 (9)
Newly developed	2 (18)
Unknown	2 (18)

(DMARDs) in all. Six patients discontinued etanercept because of good clinical response after 22 (range 13-55) months etanercept treatment. At time of discontinuation none used concomitant DMARDs or prednisone and 4 patients fulfilled criteria of inactive disease. Of the 6 patients who discontinued etanercept, 5 (83%) flared and needed to restart etanercept after a median duration of 2 months (range 19 days-10 months). After re-introduction of etanercept all patients regained a good response, and 4 patients reached inactive disease again. Discontinuation of anti-TNF-alpha treatment due to inefficacy did not occur.

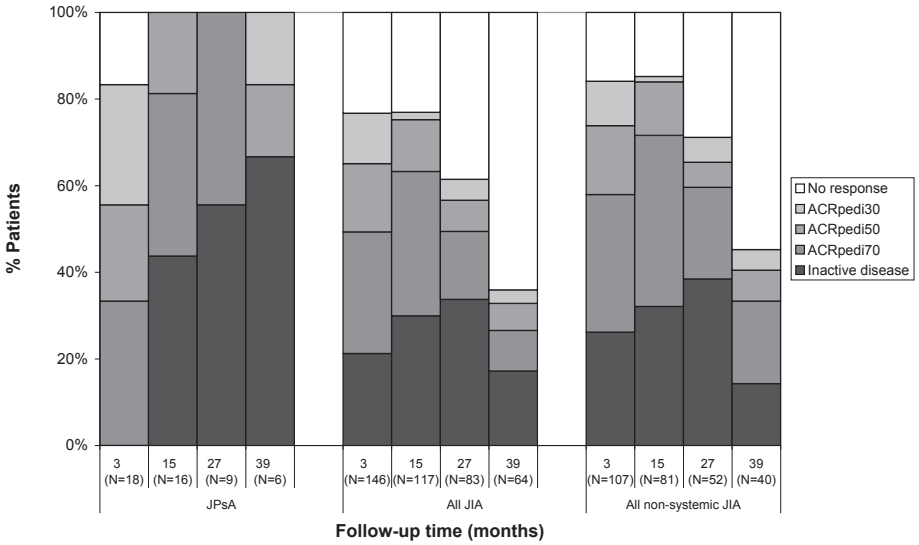

FIGURE 1. Improvement and inactive disease based on an intention-to treat modus
Percentages of juvenile psoriatic arthritis (JPsA) patients that met the criteria for the American College of Rheumatology (ACR) pedi30, -50 and -70 and inactive disease compared with the first 146 juvenile idiopathic arthritis (JIA) patients (107 non-systemic JIA subtypes) as published from our register.[5]

DISCUSSION

This is the first study to focus on the effectiveness of TNF-blockers in JPsA. Since all but one patient used etanercept, the results reflect the effectiveness of etanercept. Most JPsA patients improved rapidly, with 83% achieving an ACRpedi30 response after 3 months of treatment. This rapid ACRpedi30 response is similar to that seen in all JIA subtypes included in our register (77%) and in the German register (80%).[5, 15]
The response rate in JPsA patients increased to 100% at 15 months of treatment, indicating a delayed clinical response in some patients, as previously shown in JIA patients treated with etanercept.[16] The ACRpedi30 response seems to persist after 15 months and the percentage of patients reaching inactive disease increases to 67% in those with a follow-up of 39 months. Compared with data from our register and the German register, this current percentage of JPsA patients reaching inactive disease is substantially greater than that seen in all JIA subtypes, with 67% compared to 36% and 26%, respectively.[5, 15] Minimal differences in responses were seen between all JIA patients and all non-systemic JIA patients. Thus, even compared to non-systemic JIA patients only, TNF-blockers seem to be more effective in JPsA patients. This high first response rate has been also shown in adult-onset PsA: 37% reached remission after 18 months of treatment.[7, 17]
Meeting the criteria for clinical remission on medication has been reported as an important indicator for a sustained good clinical response after discontinuation.[18] However the majority of our JPsA patients in clinical remission who discontinued etanercept flared thereafter. This emphasizes the need to establish the optimal duration of therapy, and to develop strategies to discontinue anti-TNF-alpha treatment. It is reassuring that all patients who re-started etanercept after flaring had a good clinical response.

Surprisingly, besides the excellent effect of etanercept on joints, the psoriatic skin lesions improved in only 4 of our 9 patients with pre-existing skin lesions, and 2 patients even had a worsening of the lesions during anti-TNF-alpha treatment. However, the retrospective documentation of the course of the psoriatic skin lesions made it impossible to use validated indices (e.g. the Psoriasis Area and Severity Index). Nevertheless, it is noteworthy that, since TNF-blockade is approved for psoriasis, the pre-existing psoriatic skin lesions improved in a minority of the JPsA patients and some even worsened.
In the present study, 4 patients (2 JPsA and 2 JIA patients with other subtypes than JPsA) developed *de novo* psoriatic skin lesions after starting anti-TNF-alpha treatment. Development of new-onset psoriatic skin lesions during anti-TNF-alpha treatment has frequently been reported in adults, but only twice in children.[9-11] Whether there is a causal relation to etanercept is unclear; it could be a paradoxical adverse event, a late-

onset skin manifestations in JPsA, or a coincidental combination, since the prevalence of psoriatic skin lesions in the general population is considerable.

Classification into the JIA subtypes is based upon clinical and laboratory findings within the first 6 months after onset of JIA. Whether patients in whom the ILAR criteria changes after 6 months from onset JIA should switch to another subtype is debatable. A prospective re-evaluation of the ILAR-criteria after 6 months should be recommended, mainly since in JPsA arthritis precedes psoriatic skin lesions in about 50% of the cases and psoriatic skin lesions may occur even years after onset of arthritis.[2]

In conclusion, this is the first study to show that anti-TNF-alpha treatment is highly effective in patients with JPsA, of whom 67% reached inactive disease after 39 months of therapy. Therapy could not be discontinued in the majority of the patients. Psoriatic skin lesions improved in the minority of the JPsA patients and *de novo* psoriatic skin lesions were observed in 4 patients.

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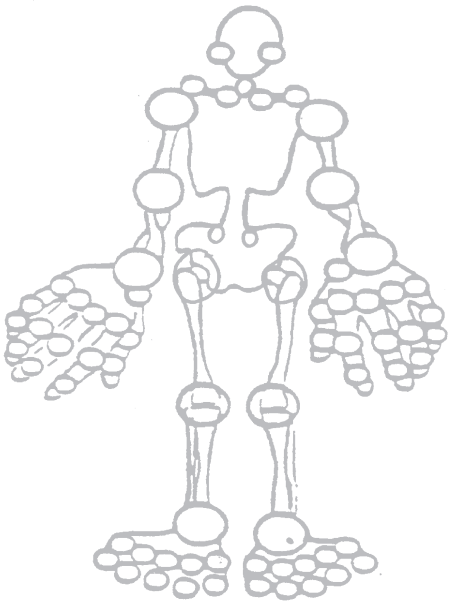
CHAPTER 3.3

TNF-alpha blocking agents for children with enthesitis related arthritis



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ABSTRACT

Objective: To evaluate the effectiveness and safety of biologic agents in children with enthesitis related arthritis (ERA).

Methods: All ERA patients in whom a biologic agent was initiated between 1999 and 2010 were selected from the Dutch Arthritis and Biologics in Children (ABC) register. In this ongoing multicenter observational register, data on the course of the disease and medication use are retrieved prospectively at start biologic agent, after 3 months, and yearly thereafter. Inactive disease was assessed in accordance with the Wallace criteria.

Results: Twenty-two ERA patients started one or more biologic agent: 20 took etanercept, two adalimumab (one switched from etanercept to adalimumab) and two infliximab (one switched from etanercept to infliximab). Characteristics: 77% male, 77% enthesitis, 68% HLA-B27-positive. The median age of onset was 10.4 (IQR 9.4-12.0) years, median follow-up from start biologic agent 1.2 (IQR 0.5-2.4) years. Intention-to-treat analysis shows that inactive disease was reached in 7 of 22 patients (32%) after 3 months, 5 of 13 patients (38%) after 15 months, and 5 of 8 patients (63%) after 27 months of treatment. Two patients discontinued etanercept due to ineffectiveness, and switched to adalimumab (inactive disease reached) or infliximab (decline in joints with arthritis after 3 months of treatment). One patient discontinued etanercept due to remission, but flared and restarted treatment, with good clinical response. No serious adverse events occurred.

Conclusion: TNF-blocking agents seem effective and safe for ERA patients previously unresponsive to one or more DMARD. However, a sustained disease-free state could not be reached, and none discontinued TNF-alpha blocking agents successfully.

INTRODUCTION

The International League of Associations for Rheumatology (ILAR) has described enthesitis related arthritis (ERA) as a subgroup of juvenile idiopathic arthritis (JIA).[1] ERA is defined as chronic inflammatory arthritis in combination with enthesitis. When either arthritis or enthesitis is absent two or more of the following criteria are required; a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain, presence of HLA-B27 antigen, onset of arthritis in a male over 6 years of age, acute (symptomatic) anterior uveitis, or history of HLA-B27 related disease in a first degree relative.[1] This ERA classification replaces previous definitions as juvenile ankylosing spondylitis (AS), seronegative enthesopathy and arthropathy (SEA)-syndrome and the more general term juvenile spondyloarthropathy. Sacroiliitis and spondylitis most often develop five to ten years after disease onset and extra-articular manifestations such as anterior uveitis occur occasionally.[2] A follow-up study demonstrated that the SEA-syndrome frequently evolves to AS; for ERA this is still unknown.[3]

Anti-TNF-alpha agents have been proven to be effective for adult-onset AS and for poly-articular course JIA.[4-10] However, the randomized controlled trials conducted in children comparing anti-TNF-alpha agents with placebo did not evaluate patients with the ERA subtype.[6, 8-9] Only a few case-series focused on the effectiveness of etanercept for patients with the ERA subtype. These studies all showed impressive improvements of etanercept on both the arthritis and enthesitis, with ACRpedi30 improvements in up to 100% of the patients and as early as 6 weeks after start of treatment.[11-13] Limitations of these studies are that most data were retrospective and with a maximum follow-up of 2 years. Until now no studies focused on other anti-TNF-alpha agent (adalimumab or infliximab) for use in this patient group. A multicentre open-label study to evaluate the effect of etanercept in the ERA subtype is pending; however, data regarding the primary outcome in a timeframe of 12 weeks are not expected until 2013.[14] The long-term effectiveness of TNF-alpha blocking agents in ERA remains unknown. Therefore we conducted this prospective study to evaluate the (long-term) effectiveness and safety of TNF-alpha blocking agents in patients with ERA.

METHODS

This study is embedded in the Arthritis and Biologics in Children (ABC) register, a multicenter prospective observational study that includes all Dutch JIA patients in whom a biologic agent is prescribed, from the first introduction in 1999. Until now more than 350 patients are included in the register. In 2008 this register was made web-based.[15] The study protocol was approved by the Medical Ethics Committee at Erasmus MC,

Rotterdam and by all participating hospitals. In the register, patient and disease characteristics are collected at baseline. Data on the course of the disease are prospectively retrieved at start, after three months of treatment and yearly thereafter until transfer to the adult care occurs. This includes the 6 variables of the JIA core set; physician's global assessment of disease activity by visual analogue scale (VAS) (range 0-100 mm, 0 best score), Childhood Health Assessment Questionnaire (CHAQ, test for functional ability) (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, the global assessment of pain by VAS was included. Data on enthesitis and sacro-iliacal involvement are not included in the JIA disease activity score and therefore lacking in our study. However, this involvement will be reflected in the physician's assessment of disease activity and the patient's or parent's assessment of wellbeing and pain.
In addition to entering follow-up data at 3 months and yearly, extra data entry times were at the time of any important events including, when biologic agents were discontinued, type of biologic switched or when there were safety concerns. Once patients discontinued their biologic agent, data collection was maintained once yearly until transfer to the adult care occurred. Safety data included adverse events (AE) and serious adverse events (SAEs; defined as life threatening or fatal events, events resulting in persistent or significant disability or events requiring intervention to prevent permanent impairment or damage, congenital anomalies, or required hospitalization or prolongation of existing hospitalization).

For our study we selected all JIA patients with the ERA subtype who started a biologic agent in the period 1999-2010, and who had at least 3 months of follow-up. For these patients we collected additional data regarding the diagnostic ILAR criteria for ERA (i.e. occurrence and location of enthesitis, presence of a history of sacroiliac joint tenderness and/or inflammatory pain, presence of HLA-B27 antigen, acute (symptomatic) anterior uveitis, and history of HLA-B27 related disease in a first degree relative).[1]

Response was assessed using the American College of Rheumatology Paediatric 30 and 70 criteria (ACRpedi 30/70). This definition states that there should be at least 30% improvement (or 70% improvement depending on the score) from baseline in three or more variables of the JIA core set with no more than one variable worsening by >30%.[16] Further, the Wallace criteria for inactive disease were used, defined as no active arthritis, no uveitis, normal ESR (values under 20 mm/hour) and a physician's global assessment of disease activity indicating no disease activity (defined as a score below 10mm).[17]

Descriptive statistics were reported as absolute frequencies or as median values with an inter-quartile range (IQR) or minimum and maximum range. We compared the patient and disease characteristics by sex and by duration of foolow-up (more or less than 1 year). Depending on the tested variable, Mann–Whitney U-test and Chi-square test were used to perform comparisons. A p-value <0.05 was considered statistically significant. SPSS version 17.0.1 was used for all analyses.

RESULTS

Patients

From 1999 through 2010, a total of 22 ERA patients used one or more biologic agent in The Netherlands. Twenty patients started etanercept as a first biologic agent, one adalimumab and one infliximab. Two patients, after failure of etanercept, switched to a second anti-TNF-alpha agent; one started adalimumab and one infliximab. No other biologic agents were introduced in this patient group. Median follow-up from start of first anti-TNF-alpha agent was 1.2 (IQR 0.5-2.4) years, with a total of 38.7 patient-years.

Patient and disease characteristics are shown in Table 1. The commonest diagnostic criteria were enthesitis (in 77% of patients), onset of arthritis in males over 6 years of age (73%), HLA-B27 antigen (68%), and sacroiliac-joint tenderness and/or inflammatory lumbosacral pain (55%). Sacroiliac-joint tenderness and/or inflammatory lumbosacral pain were not present in female ERA patients, but were present in 75% of male ERA patients (p=0.014, chi-square). There were no differences between female and male ERA patients for the remaining ERA classification criteria.

Prior to the introduction of the first anti-TNF-alpha agent, 92% of the patients used methotrexate and 77% sulfasalazine. Most patients used more than one Disease-Modifying Anti-Rheumatic Drug (DMARD) without sufficient effect.

The median duration between initiation of last synthetic DMARD and introduction of anti-TNF-alpha agent was 6.8 months (IQR 3.8-24.8 months). No patients started concomitant synthetic DMARDs in the 3 month interval before, or the 3 month interval after the start of anti-TNF-alpha blocking agents.

At the start of the first TNF-alpha blocking agent, female ERA patients (n=5) had higher CHAQ total scores (median 2.2, minimum 1.5, maximum 2.6) and higher VAS pain scores (median 88, minimum 61, maximum 96) than male ERA patients (n=17), with a median CHAQ total score of 1.1 (minimum 0.1, maximum 2.1) and a median VAS pain score of 47 (minimum 3, maximum 90) (p=0.003 and p=0.039 respectively, Mann-Whitney U-test). This difference decreased after 3 months of treatment, and disappeared after 15 months of treatment.

TABLE 1. Patient and disease characteristics (n=22)

Characteristics	N (%) or Median (IQR)
Demographic characteristics	
Male (%)	17 (77)
Median age onset arthritis in years (IQR)	10.4 (9.4-12.0)
Median disease duration before start in years (IQR)	3.1 (1.1-5.9)
Disease characteristics	
Presence of HLA-B27 antigen (%)	15 (68)
≤ 4 active joints at start anti-TNF-alpha (%)	7 (32)
> 4 active joints at start anti-TNF-alpha (%) 15 (68)	
Enthesitis (%)	17 (77)
Location Achilles tendon (%)	13 (76)
History of SI-joint tenderness and/or inflammatory lumbosacral pain (%)	12 (55)
Onset arthritis in male > 6 years of age (%)	16 (73)
Anterior uveitis (%)	0 (0)
Family history of HLA-B27-related disease (%)	12 (55)
Medication history before start anti-TNF-alpha	
NSAIDs (%)	21 (96)
Systemic glucocorticoids (%)	8 (36)
Intra-articular glucocorticoids (%)	4 (18)
Methotrexate (%)	21 (96)
Sulfasalazine (%)	17 (77)
Leflunomide (%)	2 (9)
Azathioprine (%)	1 (5)
Concomitant medications at start anti-TNF-alpha	
NSAIDs	19 (86)
Systemic glucocorticoids (%)	3 (14)
Methotrexate (%)	17 (77)
Sulfasalazine (%)	2 (9)
Leflunomide (%)	0 (0)
Azathioprine (%)	0 (0)

[TNF=tumor necrosis factor; SI=sacroilical; NSAIDs=non-steroidal anti-inflammatory drugs]

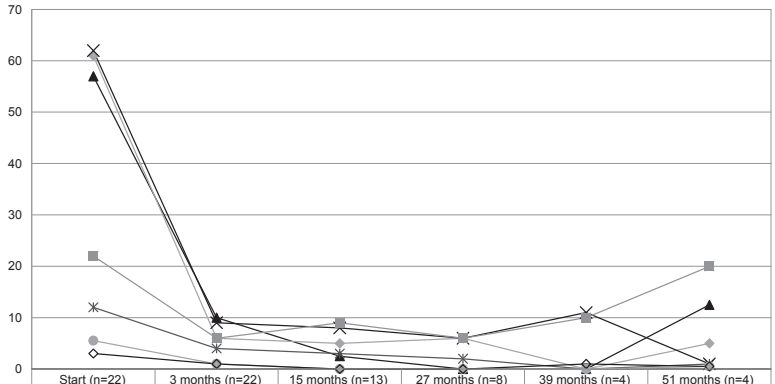
Effectiveness analysis

Figure 1 shows the disease activity scores from the introduction of first TNF-alpha blocking agent until 4 years of follow-up, on the basis of an intention-to-treat analysis.
Because of this ongoing study design (i.e. an open cohort) the total follow-up duration varied between patients. One patient was lost to follow-up after 9 months of treatment, 8 patients were transferred to adult care, and some patients started anti-TNF-alpha

agents more recently. With regard to patient and disease characteristics, the patients with more than one year of follow-up did not differ from those with less than one year of follow-up.

As figure 1 shows, the disease activity declines rapidly after initiation of the first TNF-alpha blocking agent. At 3 months of treatment, 19 of the 22 patients (86%) reached an ACRpedi30 response, and 16 of the 22 patients (73%) an ACRpedi70 response. All patients continued the anti-TNF agent after 3 months of treatment. The percentage of patients achieving ACRpedi30 and 70 responses and inactive disease at the different time-points is also shown in figure 1. One patient discontinued etanercept when remission was reached, but flared 1.3 years later and restarted etanercept with again good effect. No other patients discontinued biologic treatment.

Two patients switched to a second anti-TNF-alpha agent after failure of the first. Adalimumab was introduced in a patient after 7 months of ineffective etanercept treatment. All 22 joints that had been active before start of adalimumab treatment responded, and inactive disease was reached after only 5 months of adalimumab treatment. This



	Start (n=22)	3 months (n=22)	15 months (n=13)	27 months (n=8)	39 months (n=4)	51 months (n=4)
VAS physician	57 (32-74)	10 (0-80)	2.5 (0-25)	0 (0-70)	0 (0-31)	12.5 (0-50)
CHAQ total (x 10)	12 (1-26)	4 (0-20)	3 (0-11)	2 (0-20)	0 (0-14)	0.6 (0-9)
VAS wellbeing	61 (8-98)	6 (0-85)	4.5 (0-70)	6 (0-61)	0 (0-46)	4.5 (0-70)
VAS pain	62 (3-96)	9 (0-85)	8 (0-70)	6 (0-92)	11 (0-27)	1 (0-77)
Number active joints	5.5 (1-24)	1 (0-22)	0 (0-12)	0 (0-11)	0 (0-1)	0.5 (0-10)
Number limited joints	3 (1-16)	1.5 (0-24)	0 (0-2)	0 (0-6)	1 (0-4)	0.5 (0-4)
ESR (mm/h)	22 (2-73)	6 (1-26)	9 (1-34)	6 (2-46)	10 (2-47)	20 (2-33)
ACRpedi30 (%)	0 (0)	19 (86)	12 (92)	7 (88)	4 (100)	4 (100)
ACRpedi70 (%)	0 (0)	16 (73)	10 (77)	7 (88)	4 (100)	3 (75)
Inactive Disease (%)	0 (0)	7 (32)	5 (38)	5 (63)	2 (50)	0 (0)

FIGURE 1. Disease activity scores from introduction of first TNF-alpha blocking agent
According intention-to-treat analysis (treatment discontinuation or switching not taken into account)
Values given are median values (minimum-maximum range).
[VAS = visual analogue scale; CHAQ = Childhood Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate]

patient withdrew adalimumab temporarily due to atypical adverse events. However, after 1 month the arthritis flared and adalimumab was re-introduced, again with good response. The second patient switched to infliximab after 16 months of etanercept treatment and a remarkable decline in number of joints with arthritis (7 to 2) was seen after 3 months.
MTX could be discontinued in 4 of the 17 patients and sulfasalazine in 1 of the 2 patients who had been using it concomitantly at the start of the biologic agent. Three patients used concomitant systemic glucocorticosteroids at start and only one patient was able to stop them. No patients started systemic glucocorticosteroids during follow-up.

Safety analysis

During etanercept use, a total of 16 AEs were reported: 4 reports of mild infections, 2 fevers of unknown origin, 2 headaches, 2 injection-site reactions, 1 case of fatigue, 1 syncope, 1 transient hematochezia, 1 nosebleed, 1 report of atypical skin lesions, and 1 discordant pain sensation. This resulted in a rate of 0.45 AEs per patient-year of etanercept use.
One patient reported 6 AEs during adalimumab treatment; allergic reaction, injection-site reaction, headache, mild infections, pneumonia, and pain while breathing. Adalimumab was temporarily discontinued; however, the pain while breathing remained, and adalimumab was restarted.
No AEs were seen in the 2 patients while infliximab was being used.
No SAEs were reported during any of the anti-TNF-alpha agent treatment periods.

DISCUSSION

In our prospective observational study, we evaluated the effectiveness and safety of TNF-blocking agents in all Dutch ERA patients in the 1999-2010 period. Although all available TNF-blocking agents were included, most patients started etanercept, and these results therefore mainly reflect the effectiveness of etanercept.

A remarkable decline in all parameters of the disease activity score was seen after as few as 3 months of treatment, and all patients continued their first TNF-alpha blocking agent after 3 months of treatment. After 3 months of treatment, 19 of the 22 patients reached an ACRpedi30 response, 16 of the 22 patients an ACRpedi70 response, and one-third achieved inactive disease. This rapid and high response, not accountable to recent changes in synthetic DMARDs, is especially impressive considering the fact that these patients were previously unresponsive to one or more synthetic DMARD, and is also comparable with previously published case-series in ERA patients treated with

etanercept.[11-13] To date, for patients we have followed on therapy for 15 months (n=13) and 27 months (n=8) the response appears to be maintained. This is comparable to a publication from our register in 2009 with inclusion of all JIA subtypes.[7] However, not all patients achieved inactive disease, even though some patients were treated for many years with TNF-alpha blocking agents. No patients were able to discontinue anti-TNF-alpha agents successfully and most concomitant medications (including glucocorticosteroids) were continued during treatment. Further, the inactive disease-rate at 27 months was not sustained in the few patients with a longer follow-up. It seems that for this patient group, despite the rapid response to TNF-blocking agents, complete disease control is still difficult to achieve. This is also seen in adult-onset AS, with only one-third of patients treated with TNF-blocking agents reaching less than 20% disease activity in all four domains after 1 to 2 years of treatment.[18-20]

Switching between TNF-alpha blocking agents occurred in our study twice. Both switchers (one to adalimumab and one to infliximab after failing etanercept) improved remarkably. Until now, introduction of a second anti-TNF-alpha agent for JIA has been evaluated once. In that retrospective cohort study 73 JIA patients (one-third of the total cohort) switched to a second biologic agent.[21] The second introduced biologic agent was discontinued in 53% of the patients because of ineffectiveness or adverse events. No detailed information was given on the treatment response after initiation of the second agent. No conclusions can be drawn whether switching between biologics for ERA patients is effective; however, it seems a valuable option, especially because few alternative treatments are available.

It is remarkable that at start of anti-TNF-alpha treatment female ERA patients report higher VAS pain and CHAQ scores than males. This is in accord with a cross-sectional study of JIA patients transitioned to the adult-care showing significantly higher CHAQ scores in females with ERA.[22] In a case-control study comparing ERA with oligo-articular and poly-articular subtypes the female sex was found to be a predictor of failure to achieve remission.[23] In our study sex was not a predictor of lack of treatment response since differences in male and female patients disappeared after 15 months of treatment and the numbers are small.

Etanercept seemed to be well tolerated with a favourable safety-profile for this poorly described subset of JIA patients. Our non-serious adverse event rate of 0.45 AEs/patient-year of etanercept use seems to be higher compared to reports for all JIA subtypes with 0.09-0.21 non-serious AEs/patient-year.[5, 7] However these results should be interpreted with care, because only 38.7 patient-years of follow-up were included. No safety-profile

of adalimumab and infliximab for its use in ERA patients can be given since only 4 patients used these drugs.

Our study has some limitations. First, the number of patients included was low and the number of patients with follow-up data beyond 15 months dropped quickly. The 22 patients included in our study are all ERA patients in the Netherlands who started biologic agents in an 11-year treatment period. Though the number is small, for this indication it is the largest case-series published until now.
The second limitation is that, because our register focuses on all JIA patients in the Netherlands, detailed information about the responses of axial involvement and enthesitis was beyond the scope of our register. However, we expect that these signs will be reflected in the physician's global assessment of disease activity and patient's or parent's global assessment for wellbeing and pain. Burgos-Vargas et al. have proposed a tool for clinical evaluation for ERA containing 12 variables, including spinal and sacroiliac joint pain and tenderness and enthesitis, but this tool has not been validated yet.[24]

In conclusion, TNF-blocking agents seem effective and safe for ERA patients who previously did not responded to synthetic DMARDs. As in adults, a sustained disease-free state could not be reached, and none of the patients discontinued the biologic agents successfully. The agents' effect on enthesitis and spinal involvement remains to be determined.

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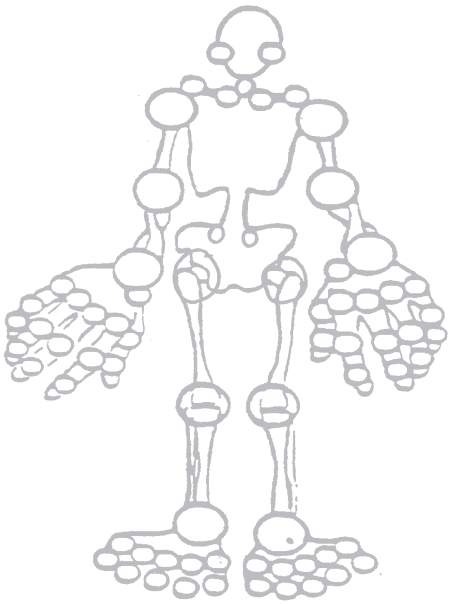
CHAPTER 3.4

TNF-alpha blocking agents in persistent oligo-articular JIA



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Submitted as:
Janneke Anink, Marieke H. Otten, Femke H.M. Prince, et al. Tumour Necrosis Factor (TNF)-blocking agents in persistent oligo-articular juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologics in Children Register

ABSTRACT

Objectives: Because tumour necrosis factor (TNF) inhibitors are not approved for persistent oligo-articular juvenile idiopathic arthritis (oJIA), however used off-label, we evaluated their effectiveness in patients with this subtype.

Methods: Patients with persistent oJIA were selected from the Dutch Arthritis and Biologics in Children (ABC) register, an ongoing multicenter prospective study, including all Dutch children with JIA using biologic agents. The response was assessed by the JIA core-set disease-activity variables and the Wallace criteria for inactive disease.

Results: Until February 2011, 16 persistent oJIA patients (68.8% female) had been included in the register. Median age at onset was 8.4 (IQR 2.1-13.5) years, 18.8% had a history of uveitis, and 56.3% were ANA-positive. All had previously used methotrexate, and 81.3% intra-articular corticosteroids. Median follow-up after introduction of biologic treatment was 13.7 (IQR 8.3-16.7) months. Fourteen patients started etanercept; adalimumab was started as first biologic in two patients who had active arthritis as well as uveitis.
Although patients with persistent oJIA had few affected joints (median of 2 active joints at start biologic (IQR 1-3), they had high patient/parent assessments of pain and wellbeing (median VAS 51 (IQR 1-64), 44 (IQR 6-66) respectively). Additionally, their physician evaluated the disease-activity as moderately high (median VAS 36 (IQR 4-65)). After 3 months this had decreased to zero (IQR 0-30) and 63% had achieved inactive disease. After 15 months the disease was inactive in 90%. TNF-inhibitors were tolerated well.

Conclusions: TNF-blocking agents seem an effective and justifiable option in persistent oJIA when treatment with intra-articular corticosteroid injections and methotrexate has failed.

INTRODUCTION

The International League of Associations for Rheumatology (ILAR) distinguishes oligo-arthritis as a one of the seven categories of juvenile idiopathic arthritis (JIA)[1], defining it as arthritis affecting four or fewer joints during the first six months of disease. On the basis of the number of joints affected after the first six months of disease, the oligo-arthritis (oJIA) category is subdivided into the persistent form (four or fewer joints) and the extended form (more than four joints) form. Persistent oJIA is a well defined subset. Typically, it is not observed in adults, and starts early, usually before the age of six, and more often in girls than boys. Patients have asymmetric arthritis, predominantly affecting knees and ankles. They have a high risk of chronic anterior uveitis (up to 30%), and antinuclear antibodies (ANA) are often present (70-80%).[2]

For many years, persistent oJIA was treated with non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections. In all JIA categories including oJIA there has recently been a tendency towards a more aggressive treatment regimen including synthetic disease modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine (SSZ) and methotrexate (MTX). The ultimate treatment goal is to achieve disease remission.

Despite such intensified treatment, this goal is not reached by all patients. Numbers of persistent oJIA patients with long term ongoing disease activity vary greatly between cohort studies.[3-6] A recent comprehensive cohort study reports long term ongoing disease activity in more than 15% of patients. The same number of patients had permanent articular or extra-articular damage.[7] Even though patients with persistent oJIA are generally thought to have the best outcome of the seven JIA categories, they are thus at risk for joint destruction and/or visual impairment.

For those patients at risk, the American College of Rheumatology now recommends adding tumour necrosis factor-alpha (TNF-alpha) blocking agents, a biologic agent, to the treatment regimen.[8] The TNF-alpha-receptor blocking agent etanercept has proved to be effective in poly-articular JIA.[9, 10] In the Netherlands etanercept is registered since 2000 for JIA patients with a poly-articular course and no response to the maximum tolerated dose MTX. In 2008 adalimumab was registered for the same indication.[11] This fully human monoclonal antibody against TNF-alpha is also used effectively in the treatment of uveitis associated with JIA.[12]

As more experience is gained with TNF-alpha blockers, these agents are now also prescribed off-label for refractory persistent oJIA. However, at present, no detailed studies have focused on their effectiveness and safety specifically in this group of JIA-patients. Therefore, the present study evaluates the effectiveness and safety of TNF-blocking agents in all Dutch patients with persistent oJIA included in the Arthritis and Biologics in Children (ABC) register until February 2011. An additional aim was to explore whether

persistent oJIA patients treated with TNF inhibitors resemble other non-systemic JIA patients (patients with all JIA categories except systemic JIA) included in the register.

METHODS

For the current study, patient data were retrieved from the ABC register, an ongoing multicenter prospective observational register which aims to include all Dutch JIA patients treated with biologic agents since 1999.[13] The register was established with the main aim of monitoring the effectiveness and safety of biologic treatment in children with JIA. The study protocol was approved by the Medical Ethics Committee at Erasmus MC, Rotterdam, and by all participating hospitals.
In the ABC register, patient and disease characteristics were collected at start of TNF-inhibitor. At the initiation of treatment, and then at three, 15 months and yearly thereafter, data on the disease activity according to the JIA core-set variables were retrieved (physician's global assessment 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 well-being and pain by VAS; number of active and limited joints and erythrocyte sedimentation rate (ESR)).
Data were also entered at the time of any important event, including discontinuation or switch of biologic agents. Infectious and non-infectious adverse events (AEs) and serious adverse events (SAEs) were reported by the treating physician on a continuous basis. The FDA definition of an SAE was used.[14] Flaring of arthritis or uveitis was not reported as an AE, but regarded as a measure of treatment response.

We selected all persistent oJIA patients, who had been included in the ABC register from its foundation to February 2011 and were treated with TNF-alpha inhibitors. All these patients fulfilled the ILAR criteria for persistent oligo-arthritis (oJIA).[1] Those without active arthritis who had started biologic treatment for uveitis were not included in this study.

We compared the patients and disease characteristics of the persistent oJIA patients with those of all other JIA patients included in our register until February 2011. For this analysis we excluded patients with the systemic subtype (n=68). The other so called non-systemic JIA patients are patients with extended oJIA, poly-articular rheumatoid factor (RF) negative JIA, poly-articular RF positive JIA, enthesitis related arthritis (ERA) and juvenile psoriatic arthritis. For the comparison we distinguished two groups: patients with four or fewer active joints and patients with more than four active joints at start of biologic treatment.

The response to treatment was assessed by evaluating the disease activity variables of the JIA core-set according to an intention to treat analysis.[15]
Inactive disease was defined as no active arthritis, no uveitis, normal ESR (values under 20 mm/h) and physician's global assessment indicating no disease activity (defined as a score below 10 mm).[16]

Descriptive statistics were reported as absolute frequencies or as medians with inter-quartile range (IQR). Fisher's exact, Kruskal-Wallis and Mann Whitney U tests were used to perform comparisons as applicable. A p-value of <0.05 was considered statistically significant. SPSS version 17.0.1 was used for all analyses.

RESULTS

Patients

Of the 408 patients included in the register until February 2011, 16 patients had persistent oJIA (4%). The first patient started anti-TNF treatment in July 2007. The majority of patients (87.5%) were initially treated with etanercept because of persistent arthritis. The two patients starting adalimumab had active arthritis as well as active uveitis. All patients were treated previously with MTX. Seven patients experienced MTX intolerance, with severe nausea and/or transaminase elevations. For these patients the maximum dose was not reached. The remaining nine patients all used MTX up to a maximum dose of $\geq$ 15 mg/m2 for more than six months. Median follow-up after the introduction of a TNF inhibitor was 13.7 (IQR 8.3-16.7) months. Median age at onset of JIA was 8.4 (IQR 2.1-13.5) years. In the majority of patients one or both knees were involved (a total of 22 knees) at some point in the disease course. Other joints that were affected were ankles (nine), elbows (three), fingers (three), hip (two), shoulder (one) and temporomandibular joint (one). For eleven patients conventional radiographs of the affected joints were available. Two of these patients had erosive deformities of the ankle joint. Two other patients had growth disturbances of the knees.
Patient and disease characteristics of the patients with persistent oJIA and the patients with other non-systemic JIA categories in the register are shown in Table 1.
Patients with persistent oJIA were characterized by a high prevalence of uveitis and ANA-positivity. The majority of patients received intra-articular corticosteroids. When patients were not treated with intra-articular corticosteroids, this was explained by a disease course dominated by severe refractory uveitis and/or arthritis in joints less accessible for injections.
Persistent oJIA patients resembled the patients with non-systemic JIA categories with four or fewer active joints at initiation of biologic therapy (extended oJIA being the most

TABLE 1. Patient and disease characteristics

Characteristics	Persistent oJIA (n=16)	Non-systemic JIA categories other than persistent oJIA	
		≤ 4 active joints at start biological (n=69)	>4 active joints at start biological (n=258)
Female (%)	11 (68.8)	44 (63.8)	185 (71.7)
Median age at onset, years (IQR)	8.4 (2.1-13.5)	6.8 (2.8-10.6)	8.3 (3.5-11.5)
Median age at start first biological, years (IQR)	12.1 (8.5-16.1)	13.4 (9.4-15.5)	12.5 (9.2-15.2)
Median JIA disease duration before start biological, years (IQR)	2.0 (1.2-6.0)	4.1 (1.8-7.9)	2.7 (1.3-5.7)
History of uveitis (%)	3 (18.8)	10 (14.5)	12 (4.7)**
ANA positivity (%)	9 (56.3)	33 (47.8)	67 (26.0)*
HLA B27 positivity (%)	2 (12.5)	10 (14.5)	16 (6.2)
RF positivity (%)	-	6 (8.7)	30 (11.6)
Category JIA			
Polyarticular RF negative	-	18 (26.1)	136 (52.7)
Πolyarticular RF positive	-	8 (11.6)	29 (11.2)
Oligoarticular persistent	16 (100)	-	-
Oligoarticular extended	-	27 (39.1)	58 (22.5)
Psoriatic arthritis	-	7 (10.1)	19 (7.4)
Enthesitis related arthritis	-	9 (13.0)	16 (6.2)
First introduced biological			
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			
NSAID (%)	15 (93.8)	68 (98.6)	250 (96.9)
Systemic corticosteroids (%)	3 (18.8)	26 (37.7)	108 (41.9)*
Intra-articular corticosteroids (%)	13 (81.3)	36 (52.2)*	59 (22.9)**
Methotrexate (MTX) (%)	16 (100.0)	68 (98.6)	238 (92.2)
Other DMARD besides MTX (%)	2 (12.5)	9 (13.0)	52 (20.2)
Co-medication at start biological			
NSAID (%)	7 (43.8)	46 (66.7)**	217 (84.1)**
Systemic corticosteroids (%)	-	8 (11.6)	70 (27.1)*
Intra-articular corticosteroids (%)	3 (18.8)	7 (10.1)	7 (2.7)*
Methotrexate (%)	10 (62.5)	50 (72.5)	231 (89.5)**
Other DMARD besides 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)**
CHAQ total	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 wellbeing	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)

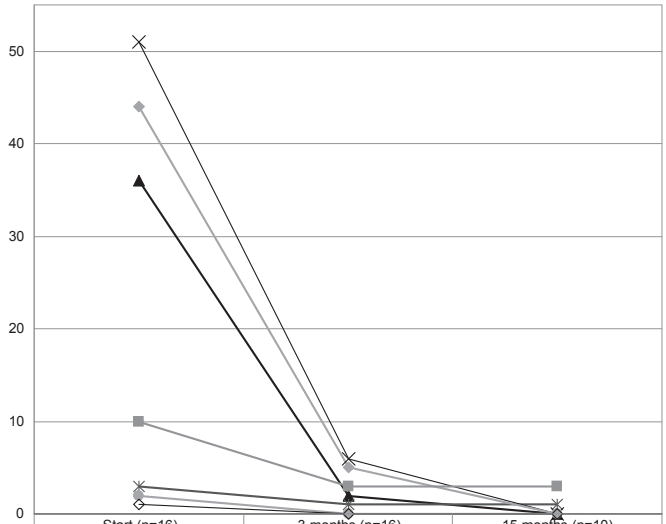
* p≤0.05, ** p≤0.001, persistent oJIA patients compared to the two groups of other non-systemic JIA patients.
[JIA, juvenile idiopathic arthritis; IQR, inter-quartile range; ANA, anti-nuclear antibodies; RF, rheumatoid factor; NSAID, non-steroidal anti-inflammatory drug; DMARD, disease modifying anti-rheumatic drug; VAS, visual analogue scale; CHAQ, Childhood Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate]

common JIA-category in this group) on most characteristics. The age at onset of the disease was the comparable in all groups.

All patients with other non-systemic JIA categories had higher disease activity and were treated more extensively (with oral corticosteroids and other DMARDs besides MTX) than the persistent oJIA patients.

Effectiveness

Figure 1 shows the response to treatment in patients with persistent oJIA during the first fifteen months of treatment. All disease activity variables were elevated at baseline and decreased within three months, except for ESR, which remained within normal range. An even greater decrease could be seen after fifteen months of follow-up. Inactive disease was reached by ten patients (63%) within three months. Ten patients had more than 15 months of follow-up, nine of these patients (90%) achieved inactive disease. There was no difference between the response to adalimumab (two patients) and etanercept.



	Start (n=16)	3 months (n=16)	15 months (n=10)
VAS physician	36 (4-65)	2 (0-13)	0 (0-30)
Total CHAQ score x10	3 (0-9)	1 (0-10)	1 (0-6)
VAS pain	51 (0-71)	6 (0-75)	0 (0-34)
VAS wellbeing	44 (0-74)	5 (0-75)	0 (0-20)
Number of active joints	2 (1-4)	0 (0-1)	0 (0-2)
Number of limited joints	1 (0-3)	0 (0-2)	0 (0-2)
ESR	10 (2-60)	3 (2-30)	3 (2-29)
Number of patients with inactive disease (%)	0 (0)	10 (62.5)	9 (90)

FIGURE 1. Change in median value of disease activity variables

All variables presented in median with range.

VAS, visual analogue scale; CHAQ, childhood health assessment questionnaire; ESR, erythrocyte sedimentation rate

Three patients received intra-articular corticosteroids concurrent with the start of etanercept. These patients had been treated with intra-articular corticosteroids in multiple joints before, with insufficient sustained response. All three patients achieved inactive disease within three months which sustained for the observed follow-up in one patient (14 months). The other two patients both had a disease flare after ten months, of which one patient was treated with another corticosteroid injection. The other had just discontinued etanercept treatment and subsequently restarted. No other patients were treated with intra-articular steroids during anti-TNF treatment.
One patient switched from etanercept to adalimumab after incomplete response to etanercept and achieved inactive disease. Other discontinuation of TNF inhibitors because of ineffectiveness did not occur. Two patients discontinued treatment because of disease remission, one being described in the above section. The second patient discontinued treatment after ten months, and showed lasting remission during the observed follow-up after stopping etanercept (four months).

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. Nine adverse events (AEs) were reported during etanercept use, of which two serious adverse events (SAEs) (one patient with a restrictive pulmonary function and one patient with a perforated appendicitis). This resulted in an AE-rate of 0.44/patient-year and an SAE-rate of 0.12/patient-year on etanercept. No AEs were reported during adalimumab use. TNF-inhibitors were temporarily discontinued four times because of an infectious event. No permanent discontinuation because of AEs occurred.

DISCUSSION

This is the first study that extensively evaluates the effectiveness and safety of TNF blocking agents in patients with persistent oJIA. The majority of patients started etanercept, thus our results mainly reflect the effectiveness of etanercept. Disease activity declined rapidly after introduction of a TNF blocking agent. This result was maintained and even improved after fifteen months, with almost all of the patients with available follow-up achieving inactive disease. This decrease in disease activity was similar to results in patients included in our register with other (non-systemic) categories of JIA.[10] This observed effectiveness is promising for patients with persistent oJIA, who were previously unresponsive to DMARDs and intra-articular corticosteroids.
A recently published observational study of patients with all JIA categories using etanercept reports on 38 patients with persistent oJIA (5% of the total studied popula-

tion). This study focused on disease remission and adherence to therapy. Of these oJIA patients 53% achieved inactive disease and 13% remission on medication.[17] No further patient or disease characteristics are described and details on follow-up duration were not provided, but follow-up was at least six months. We observed a higher percentage of inactive disease, albeit in a smaller number of patients.

In general only JIA patients with poly-articular course JIA unresponsive to the maximum tolerated dose of MTX are considered candidate for anti-TNF therapy. Despite this, paediatric rheumatologists prescribe TNF blocking agents to a small group of patients with persistent oJIA. Most of these started TNF-alpha inhibitors because of ongoing arthritis, however for the two patients who received adalimumab the presence of refractory uveitis contributed to the decision to prescribe the TNF inhibitor.

When we compare the patients with persistent oJIA who were treated with TNF inhibitors with persistent oJIA patients described in the literature, we notice that there are some differences in patient characteristics. Persistent oJIA patients characteristically have an onset of the disease before 6 years of age, while our patient group had a median onset age of 8.4 years. The prevalence of ANA-positivity (56.3%) was high, but lower than might have been expected based on numbers usually reported in persistent oJIA (70-80%).[2] Summarizing, the persistent oJIA patients described in this report represent a specific subset.

The categorization of JIA is subject to an ongoing debate and classifying JIA by other factors than number of joints at onset has been proposed. ANA positivity has been suggested as a potential classifying factor, clustering patients with oligo-articular and poly-articular course into a new more homogeneous subgroup.[18, 19] The goal of categorization is to identify homogeneous subgroups and adapt treatment strategy accordingly. In the recently developed ACR recommendations for management of JIA, treatment choice is not purely based on JIA category, but rather on disease activity, prognostic features and response to previous therapy.[8] TNF inhibitors are recommended in patients with a history of fewer than four active joints when disease severity is moderate or high, poor prognostic features are present and the patient was treated with 15mg/m2 parenteral MTX without sufficient result.

According to the ACR recommendations, 12 of our patients had moderate disease activity and six also had poor prognostic features. Thus, six of our patients were treated with TNF inhibitors in line with the ACR recommendations. It seems that in daily practice these recommendations are not fully applicable. In our study the patients not fulfilling the criteria for anti-TNF treatment according to the recommendations all had ongoing recurrent arthritis with similarly high patient/parent assessments of pain and wellbeing as other patients treated with TNF inhibitors. Therefore, when all available treatment

options have been tried, and nevertheless the disease relapsed, treatment with TNF inhibitors can also be considered in patients with persistent oJIA.

A reason to be reticent with prescription of TNF inhibitors to patients with persistent oJIA may be a concern about safety. The safety profile of these agents in this study seems favourable, however, only 16 patient-years have been observed, of which only 2.2 patient-years for adalimumab. Although TNF blockers are observed to be well tolerated in previous reports on patients with all JIA subtypes[10, 20], there is still insufficient knowledge about the long-term effects. Balancing the risks and benefits remains important when considering treatment with TNF blockers.

In the present report the response to treatment was evaluated by a change of the core-set disease activity variables. At the moment no specific instrument evaluating oligo-articular patients is available. We chose not to use the ACR Pedi 30, 50, 70 response criteria, which in our opinion are more appropriate to poly-articular disease and do not capture the full degree of change in disease activity when individual variables are low or even in normal range at baseline, as is the case in persistent oJIA. The juvenile arthritis disease activity score (JADAS) is a recently developed composite score for assessing disease activity in JIA.[19] It uses only joint counts, ESR and the physician global assessment of disease activity. To our opinion, however, for evaluating persistent oJIA patients measures should depend less on ESR and possibly more on the global assessment by the physician and the parent/patient global assessment of wellbeing, which are the variables of the JIA core-set most responsive to change.[21] Another option could be to use weighted joint counts, which correlate better with these subjective measures.[22]

The present study has some limitations. Most important is the small number of patients. In addition only a small number of patients had a follow-up more than fifteen months. The 16 patients included in this study were the only persistent oJIA patients in the Netherlands initiating TNF blocking agents since the introduction of this medication. To our knowledge this is the largest case series to date, focusing only on patients with persistent oJIA and reporting detailed information on these patients.

In our study, no data are reported on persistent oJIA patients treated with anti-TNF inhibitors only for uveitis. The ABC register is designed to record disease activity data on arthritis and patients without arthritis with only uveitis are beyond the scope of our register.

Three of our patients were treated with intra-articular corticosteroids at start of etanercept and subsequently achieved inactive disease within three 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. We can only speculate on how inactive disease was obtained in these three patients.

From our results it seems that etanercept did contribute to lowering disease activity in these patients.

The results of the current study suggest that TNF blockers are effective in persistent oJIA refractory to MTX treatment and intra-articular corticosteroid 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, and therefore differ from the classic persistent oJIA patients. Larger studies are needed to identify factors that characterize these more severely affected persistent oJIA patients, in whom treatment with TNF inhibitors is a justifiable option.

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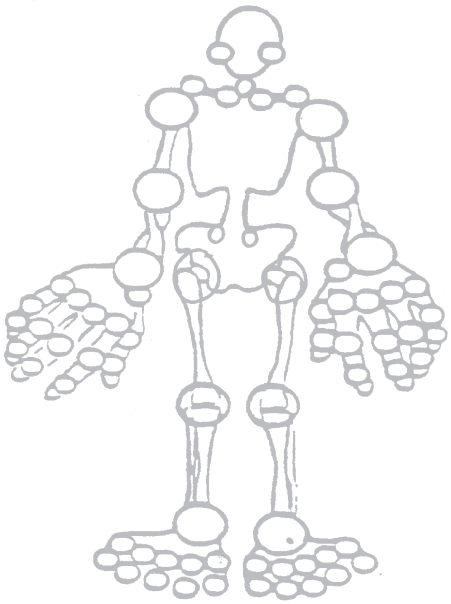
CHAPTER 3.5

Long-term effects of etanercept on growth and bone mineral density in JIA



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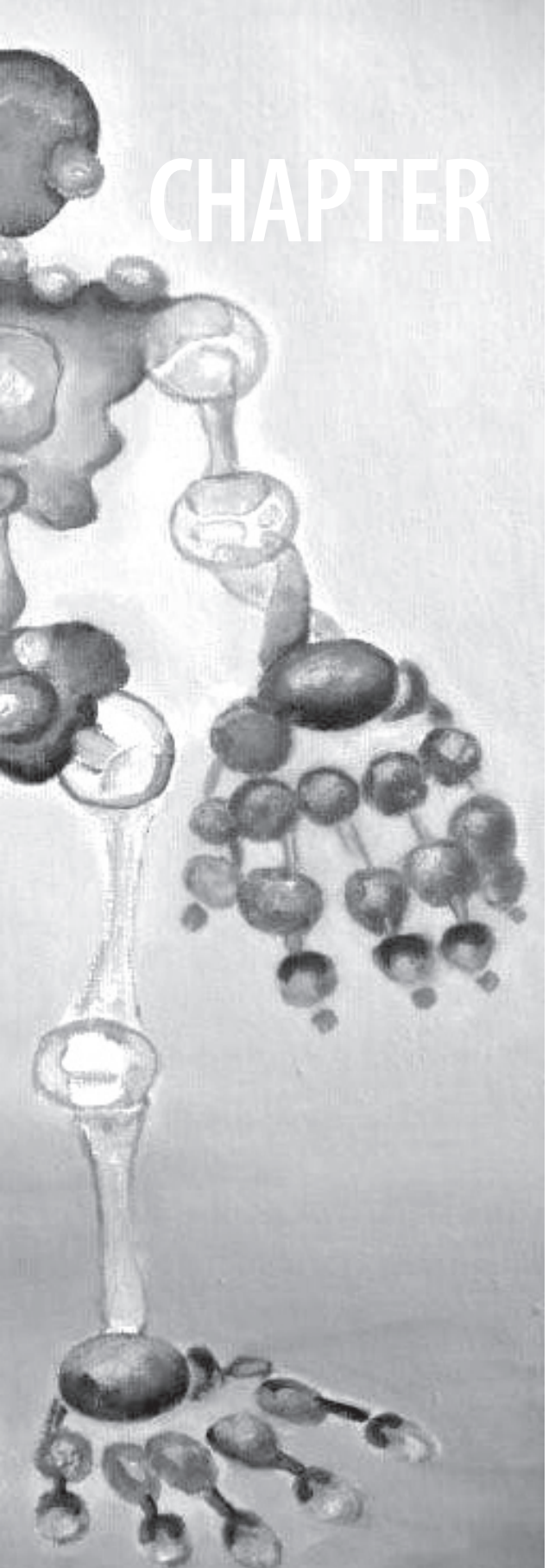
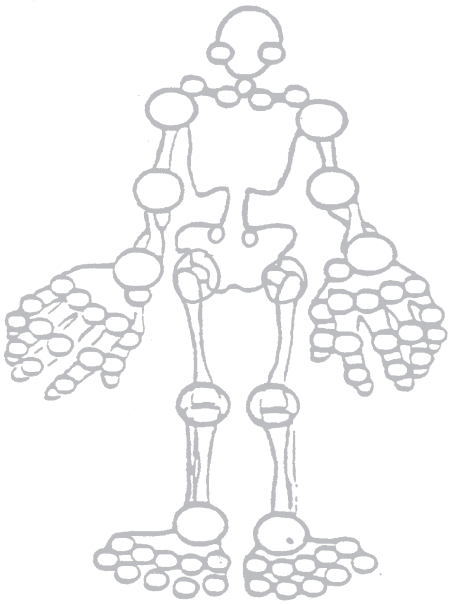


CHAPTER 4

What to do after failing etanercept in JIA?

CHAPTER 4.1

Delayed clinical response in patients with JIA treated with etanercept



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ABSTRACT

Objective: To evaluate response in patients with juvenile idiopathic arthritis (JIA) who failed to meet response criteria after 3 months of etanercept treatment.

Methods: This was a prospective ongoing multicenter observational study of all Dutch patients with JIA using etanercept. Response according to American College of Rheumatology Paediatric 30 criteria was assessed at study start and at 3 and 15 months.

Results: In total we studied 179 patients of median age 5.8 years at disease onset; 70% were female. Thirty-four patients did not respond after 3 months, of which 20 continued etanercept and 11 achieved response thereafter.

Conclusion: The delayed clinically relevant response in a substantial proportion of patients who initially did not respond justifies the consideration of continuing therapy to at least 6 months.

INTRODUCTION

For patients with juvenile idiopathic arthritis (JIA) resistant to conventional agents, treatment with biologic therapies such as etanercept is a valuable option. Studies showed rapid improvements achieved with etanercept, but the optimal duration of therapy to evaluate effectiveness in JIA is still unknown.[1-4] Improvement should be expected before 3 months of treatment for rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) and for both RA and JIA according to the 2007 consensus group findings.[5,6] The British Paediatric Rheumatology Group advises withdrawal of biologic agents in the event of lack of response after 6 months of treatment.[7] Due to the guidelines and to the coverage regulations for health insurance, response in The Netherlands is evaluated at 3 months.

Several studies in adults show that a substantial proportion of patients with RA who failed to reach the response criteria at 3 months, and continued treatment, achieved response at 6 months, indicating a time lag in clinical efficacy.[8-10] JIA patients in whom a delayed response was seen at 6 months are mentioned by Lovell, *et al*, although no details were given.[11]

Our objective was to evaluate clinical response to etanercept in patients with JIA who failed to meet the response criteria at 3 months.

PATIENTS AND METHODS

This study was embedded in the Arthritis and Biologics in Children project, a prospective, continuing, multicenter observational study that includes all Dutch JIA patients using etanercept since its introduction in 1999.[3] Since 2008 a Web-based register has been used.[12] The study protocol was approved by the Medical Ethics Committee of Erasmus MC, Rotterdam, and participating hospitals. In The Netherlands, patients with polyarticular course JIA are eligible for treatment if the disease is active despite maximum (tolerated) dose of methotrexate (MTX). The decision to continue the reimbursement is based on objective signs of improvement, taking into account other arguments from the treating physician such as phasing out co-medication.

In the register, patient and disease characteristics are collected at baseline. Data regarding the course of the disease are retrieved at start of therapy, at 3 months, and yearly thereafter, including variables of the JIA disease activity score: physician's global assessment of disease activity by visual analogue scale (VAS; range 0–100 mm, 0 = best score); Childhood Health Assessment Questionnaire (range 0–3, 0 = best score) by patients/parents, including global assessment of well-being by VAS; number of active and limited joints; and erythrocyte sedimentation rate.

Patients with a follow-up of at least 15 months were selected up until November 2008. Response was assessed using the ACR Paediatric 30, 50, and 70 criteria (ACRpedi30, 50, 70), defined as at least 30% (50%, 70%) improvement from baseline in 3 variables of the JIA core set, with no more than one of the remaining variables worsening by > 30%.[13] We used the definition of inactive disease according to Wallace, *et al.*[14] We defined initial non-responders as patients not achieving ACRpedi30 response after 3 months' treatment and secondary responders as initial non-responders who continued treatment, and achieved an ACRpedi30 response later during follow-up.

RESULTS

There were 179 patients eligible for inclusion, 70% female, with median age at onset of JIA 5.8 years (interquartile range 3.0-10.0 yrs) with subtypes as summarized in Table 1.

TABLE 1. Characteristics of initial responders, secondary responders and non-responders.

Total N=179	Initial responders (N=145)	Secondary responders (N=11)	Non-responders (N=23)
Female : Male	101 : 44	5 : 6	20 : 3
Median age onset JIA (years (IQR))	6.3 (3.1-10.0)	5.6 (3.4-10.0)	4.7 (2.7-5.3)
Median duration diagnosis to start etanercept (years (IQR))	3.5 (1.7-7.8)	4.0 (3.3-6.6)	3.1 (1.9-8.7)
JIA subtype			
Systemic JIA (N=42)	26 (62%)*	2 (5%)	14 (33%)
Polyarticular RF- (N=71)	63 (89%)**	3 (4%)	5 (7%)
Polyarticular RF+ (N=13)	11 (85%)	0 (0%)	2 (15%)
Oligoarticular extended (N=37)	31 (84%)	4 (11%)	2 (5%)
Psoriatic arthritis (N=10)	9 (90%)	1 (10%)	0 (0%)
Enthesitis related arthritis (N=6)	5 (83%)	1 (17%)	0 (0%)

Response according to the American College of Rheumatology Pediatric 30 Response criteria (ACRpedi30). [JIA = Juvenile Idiopathic Arthritis; RF- = rheumatoid factor negative, RF+ = rheumatoid factor positive; IQR = Inter Quartile Range]

* More Systemic JIA patients are non responders at 3 months compared to other subgroups ($p<0.001$, chi-square)

** More Polyarticular JIA RF- patients are initial responders compared to other subgroups ($p=0.03$, chi-square)

The disease course of the included patients is shown in Figure 1. Initial non-responders were 5 patients in whom etanercept was withdrawn before 3 months of therapy, because of progression of the disease or serious adverse events, and 29 patients who did

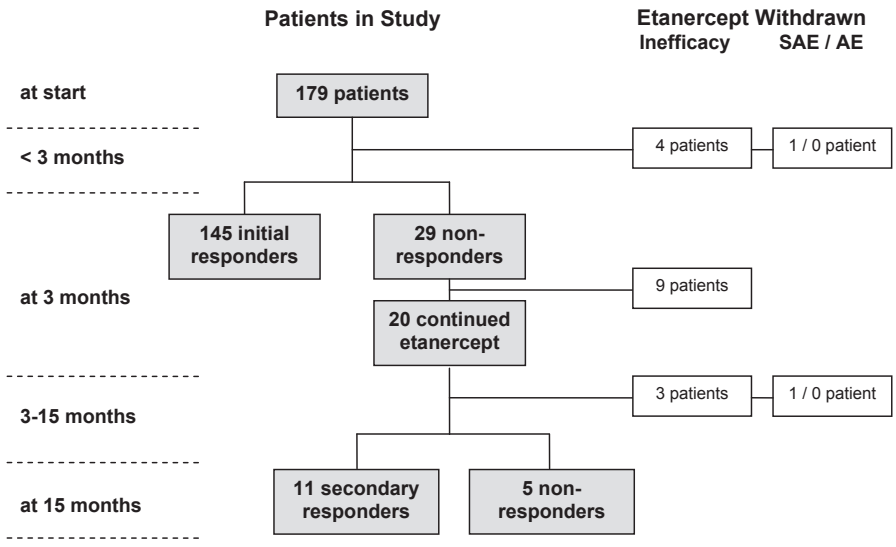

FIGURE 1. Disease course of included patients
[SAE = serious adverse event, AE = adverse event]

not meet the ACRpedi30 criteria at 3 months of treatment. In 20 of those 29 patients, the decision was made by the treating physician to continue etanercept and 11 responded thereafter. Of these 11 patients, 91% showed ACRpedi50 and 73% showed ACRpedi70 response; 36% achieved inactive disease at 15 months. None started or raised the dosage of MTX or systemic prednisone during etanercept treatment, and in the majority co-medication was discontinued (MTX in 75% and prednisone in 67% of the patients who used it). Seven percent of all responders were secondary responders. For the initial 145 responders, efficacy analysis according to intention to treat resulted in the following responses at 3 and 15 months, respectively: ACRpedi30 in 100% and 92%, ACRpedi50 in 86% and 90%, ACRpedi70 in 66% and 77%, and inactive disease in 22% and 38%. Ten patients stopped etanercept between 3 and 15 months due to remission (n=1), inefficacy (n=6), or (serious) adverse events (n=3).

Characteristics of initial responders, secondary responders, and non-responders as well as association of initial responses with subtypes are shown in Table 1. The number of secondary responders was too small to allow analysis of relations.

DISCUSSION

Our study shows that in patients with JIA a substantial proportion (55%) of non-responders at 3 months of treatment who nevertheless continued etanercept achieved a response thereafter. In adults this time lag in clinical efficacy is also seen, with a "delayed" response of up to 57% at 6 months in patients that continue treatment despite insufficient initial response.[8-10] That the delayed responders achieved relevant improvement is shown by high percentages of ACRpedi50 and ACRpedi70 responses and even inactive disease in 36%, and by the fact that co-medication was phased out in the majority of the patients. These results are similar to those of the initial responders at 15 months. From data available in our register, we examined improvement at 3 and 15 months of treatment. However, the majority of the secondary responders will have achieved response before 15 months. We recently decided to add an evaluation to our register protocol at 6 months for a better analysis. The decision to continue etanercept despite failure to achieve an ACRpedi30 response will have been made with supporting arguments from the treating physician. The initially non-responding patients who continued etanercept are therefore likely to have shown at least some improvement at 3 months. European and American guidelines limit the duration of biologic agents in case of non-response because of possible (serious) adverse events, unknown long-term effects, and high costs, although recent data on the long-term safety of etanercept show a low rate of serious adverse events.[2-4] However, etanercept is a valuable option for patients previously not responding to other second-line agents, including MTX. The increase in response observed in our study is therefore important.

In conclusion, in patients with JIA a substantial proportion of non-responders at 3 months who continue etanercept eventually show a clinically relevant improvement. Especially in patients with a partial initial response we advise consideration of continuation of treatment to at least 6 months. Recommendations in the current guidelines should be adapted accordingly.

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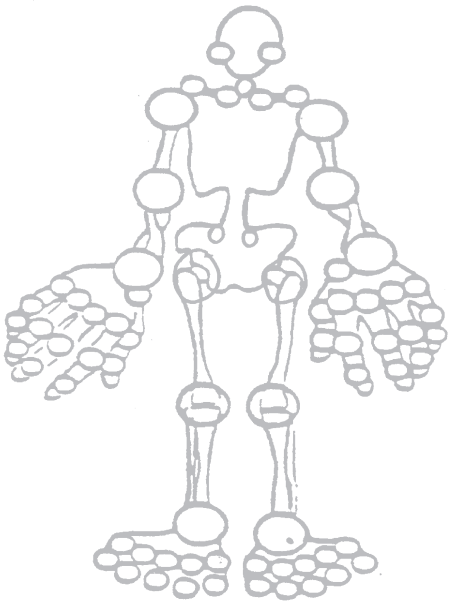
CHAPTER 4.2

Switching between biologic agents after failing etanercept; is it effective and safe in JIA?



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Submitted as:

Marieke H. Otten, Femke H.M. Prince, Janneke Anink, et al. Effectiveness and safety of a second and third biologic agent after failing etanercept in juvenile idiopathic arthritis; Results from the Dutch national ABC Register

ABSTRACT

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

Methods: The ABC register (observational cohort) includes all Dutch JIA patients who use or previously used biologic 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-naïve JIA patients who started etanercept, 80 (26%) switched to a second, and 22 (7%) to a third biologic. During 1,030 patient-years of follow-up after introduction of etanercept, 49 switches to adalimumab, 28 infliximab, 17 anakinra, 4 abatacept, and 4 trial drugs were evaluated. Eighty-four percent (95% CI, 80-88%) of patients who started etanercept as a first biologic were, after 12 months, still on the drug, compared with 47% (95% CI, 35-60%) of patients who started a second, and 51% (95% CI, 26-76%) of patients who started a third biologic agent. Patients who switched because of primary ineffectiveness seemed to continue the second agent less often (32%, 95% CI 12-53%). After etanercept failure, drug continuation of adalimumab was similar to infliximab for patients with non-systemic JIA categories; anakinra was superior to a second TNF-blocker for systemic JIA. AE-rates within first 12 months after initiation were for each course and each biologic comparable.

Conclusions: Switching to another biological agent is common, especially for systemic JIA patients. Because a second (and third) agent was less effective than the first, choosing the right first biologic is important. The choice of second biological depends on 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, around 10-22% of previously biologically-naive JIA patients discontinued etanercept within 12 months because of a lack of effectiveness or intolerance.[1-3] Different biologic agents targeting different cytokines are available nowadays. Tumour necrosis factor (TNF)-alpha antagonists are the most often prescribed biologic agents for JIA patients. Etanercept (approved since 1999), adalimumab (approved since 2008) and infliximab (not approved for JIA, but used off-label) all antagonize TNF-alpha, but have different mechanisms of action.[4-5] Therefore treating physicians consider a switch to a second TNF-alpha antagonist after failing the first. Besides these TNF-alpha antagonists, abatacept (a selective T-cell co-stimulation modulator) has been approved in 2010 for JIA patients who failed at least one synthetic disease-modifying anti-rheumatic drug (DMARD) and a TNF-alpha 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.[6-10]

Besides a few case-series, only one larger observational study regarding switching between TNF-alpha blocking agents in JIA has been published until now.[1, 11-14] This retrospective chart review from Tynjala et al. mainly described patients switching from etanercept to infliximab (and visa versa) and concluded that a switch to a second anti-TNF-alpha agent was a reasonable option.[1] 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 for Rheumatology (ACR) recommended in 2011 equally a second TNF-alpha inhibitor or abatacept for poly-articular JIA patients who failed the first TNF-alpha inhibitor. For the systemic category with active arthritis they recommended a switch from anakinra to etanercept, or visa versa, or a switch to abatacept.[15]

Since evidence with regard to switching in JIA is scarce, we evaluated the effectiveness and safety of switching to other biologic agents after failing etanercept during a long follow-up period.

PATIENTS AND METHODS

Study design and subjects

This study was part of a multicenter prospective observational register; the Arthritis and Biologics in Children (ABC) register. This register aims to include all Dutch JIA patients who use or previously used biologic 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.[16] These data included the variables of the JIA disease activity score (i.e. 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). ACRpedi 50 response criteria during etanercept exposure were calculated, which has been defined as at least 50% improvement in 3 or more variables of the JIA core set and a worsening of no more than one variable by more than 30%.[17]

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 biologic agents and adverse events (AEs).

For this study we selected all JIA patients who started etanercept as a first biologic agent before January 1st 2010, to allow for sufficient follow-up. The reported switches were restricted to the introduction of a second and third biologic agent, because only in a small number of patients a fourth agent was introduced. Switches to trial drugs were mentioned, however, outcomes of patients switching to drug trials had to be excluded from the analyses. Reasons for switching were recorded and categorized into: primary non-response, loss of response or partial response (defined as achievement of the ACRpedi 50 criteria at least once during exposure with etanercept), intolerance/adverse events (AEs), uveitis, and other reasons.

Effectiveness

As a proxy for effectiveness of treatment, drug adherence until discontinuation due to ineffectiveness of treatment, adverse events 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 time of last study visit. This drug continuation was estimated for the first, second and third introduced biologics and

for the different biologics introduced in systemic JIA and non-systemic JIA categories separately.

Furthermore, inactive disease was analyzed only for those patients who switched to another biologic agent because of ineffectiveness (primary and loss of 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 ≤ 10 mm.[18]

Safety

All medically important infectious and non-infectious adverse events (AEs) and all serious adverse events (SAEs, defined according to the FDA) 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 SAEs) and the SAE-rates per patient-year within the first year after initiation of a biologic, accounting for possible discontinuation of the biologic. We considered infections that recurred within a patient as separate AEs, but non-infectious AEs that recurred were counted only once. We reported these AE-rates and SAE-rates for all three courses of biologics and for each specific biologic agent separately.

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 3 of the 6 JIA core set variables were present the remaining values of the core set were imputed.

Descriptive statistics were reported as absolute frequencies, or as median values with an interquartile range (IQR). Logistic regression was performed to indentify baseline factors associated with patients that switched compared with patients that never switched, adjusted for follow-up duration since start 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 second biologic. P-values were calculated with the Wald's test; results are presented as odds ratios (OR) with 95% CIs.

Differences in drug continuation (according to Kaplan-Meier) were defined by the Log-rank test when comparing 2 groups and by the Log-rank Mantel-Cox when comparing multiple groups. All reported p-values were based on 2-sided tests for significance, and p-values <0.05 were considered statistically significant. SPSS version 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 a second, and 22 (7%) to a third biologic agent. Patient and disease characteristics are listed in Table 1. A total of 1,030

TABLE 1. Patient and disease characteristics before start etanercept

	JIA patients that never switch (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 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 DMARDs	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 (interquartile range)
* Patients who switched to a third agent are also represented in the switchers to a second agent patient group
** P-value < .0001 (switchers compared with patients that never switch)
*** P-value < .05 adjusted for follow-up duration (switchers compared with patients that never switch)
[JIA=juvenile idiopathic arthritis; RF=rheumatoid factor; DMARDs=disease-modifying anti-rheumatic agents; VAS=visual analogue scale; CHAQ=child health assessment questionnaire; ESR=erythrocyte sedimentation rate]

years (median of 33 months per patient) of follow-up after etanercept introduction were observed. The follow-up duration since start etanercept was significantly longer for patients that switched than for patients that never switched. Adjusted for follow-up duration, patients who switched to a second biologic were more likely to have the systemic subtype, had shorter disease duration before start etanercept and were younger at start of first biologic and, at start of etanercept, had higher CHAQ scores. Reasons for a switch to a second or third biologic agent are reported in Table 2. Ineffectiveness of treatment was the most frequently reported reason for both switches.

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 biologic and introduction of another biologic agent, 21 patients started the second agent after a median treatment pause of 14 (IQR 3-39) months, and 10 patients started the third agent after a median treatment pause of 11 (IQR 4-28) months. Median follow-up duration since start of the second biologic was 18 (IQR 7-38) months, and since start of the third 14 (IQR 6-35) months.

The drug survival of the first, second and third introduced biologic agents are reported in Figure 1. Eighty-four percent (95% CI, 80-88%) of patients who started etanercept as a first biologic were, after 12 months, still on the drug, compared with 47% (95% CI, 35-60%) of patients who started a second biologic, and 51% (95% CI, 26-76%) of patients who started a third biologic agent.

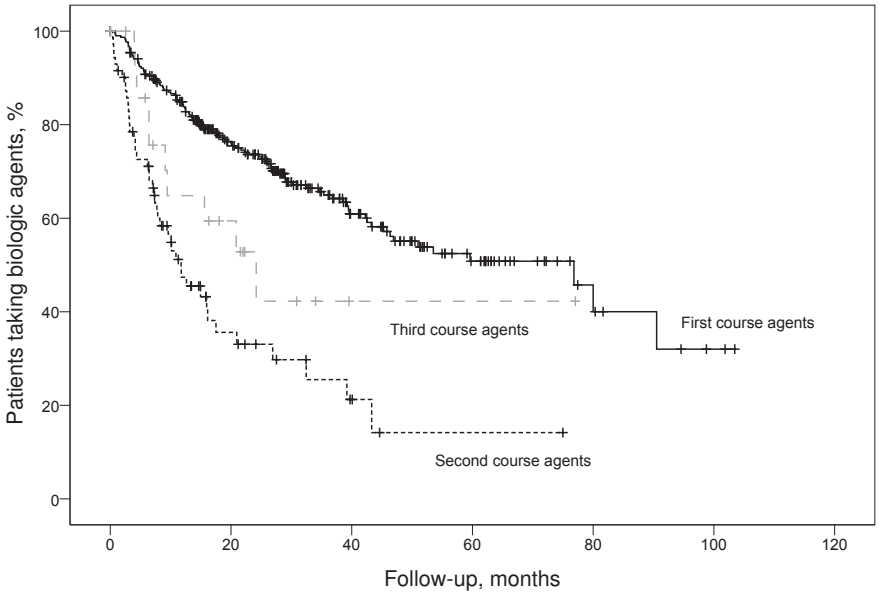

FIGURE 1. Drug continuation of first, second and third course biologics
Kaplan-Meier estimate of overall drug continuation until discontinuation of the first, second and third introduced biological agent due to ineffectiveness, adverse events or non-compliance. Vertical lines indicate censoring (censoring 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 3 courses of biological agents.

Table accompanying figure:

	N of patients	N of patients with events	N of patients censored
First course (etanercept)	307	107	200
Second course	78*	44	34
Third course	19**	9	10

* 2 patients who used a trial drug as second biological had to be excluded
** 2 patients who used a trial drug as third biological had to be excluded

Switching patterns

The majority of patients with non-systemic JIA categories switched between anti-TNF-alpha agents only (Table 3a). These patients discontinued adalimumab because of ineffectiveness or adverse events in 21 of the 42 times it was started as second/third biologic, and infliximab in 9 of the 21 times it was started as second/third biologic. Drug survival of the adalimumab courses in JIA patients with non-systemic JIA categories (50% on drug after 12 months, 95% CI 32-67%) was not different compared with the infliximab courses (54%, 95% CI 28-79%, log-rank p=0.50, Figure 2A). Four patients that switched from etanercept to adalimumab switched back to etanercept.

TABLE 3A. Switching patterns for JIA patients with non-systemic JIA categories (n=56)

			→ *Switch to 3rd biological agent:*						
			No 3rd switch	Etanercept	Adalimumab	Infliximab	Anakinra	Abatacept	Trial drug
1st biological: etanercept	→ *2nd biological:*	N_{total}							
	Adalimumab	38	28	4	N.A.	5	-	1	-
	Infliximab	16	11	-	4	N.A.	-	1	-
	Anakinra	0	-	-	-	-	N.A.	-	-
	Abatacept	2	2	-	-	-	-	N.A.	-
	Trial drug	0	-	-	-	-	-	-	N.A.
	Total	56	41	4	4	5	0	2	0

TABLE 3B. Switching patterns for systemic JIA (n=24)

			→ *Switch to 3rd biological agent:*						
			No 3rd switch	Etanercept	Adalimumab	Infliximab	Anakinra	Abatacept	Trial drug
1st biological: etanercept	→ *2nd biological:*	N_{total}							
	Adalimumab	4	1	-	N.A.	2	1	-	-
	Infliximab	4	2	-	-	N.A.	2	-	-
	Anakinra	14	7	2	2	1	N.A.	-	2
	Abatacept	0	-	-	-	-	-	N.A.	-
	Trial drug	2	1	-	1	-	-	-	N.A.
	Total	24	11	2	3	3	3	0	2

N.A. = not applicable

Interpretation table 3. For example Table 3A, first row: A total of 38 patients switched from etanercept to adalimumab. Twenty-eight of these 38 patients did not start a third biological; 4 patients started etanercept, switched to adalimumab, and switched back to etanercept; 5 patients started etanercept, switched to adalimumab, and thereafter switched to infliximab; and 1 patients started etanercept, switched to adalimumab, and thereafter switched to abatacept.

The switching patterns of systemic JIA patients are reported in Table 3b. Systemic JIA patients most often started anakinra after etanercept failure (17 times of anakinra as second/third biologic). Infliximab and adalimumab were both introduced 7 times as second/third biologic. Two patients that switched from etanercept to anakinra, switched back to etanercept again. All systemic JIA patients that started adalimumab discontinued it due to ineffectiveness or intolerance, 6 of 7 patients (86%) discontinued infliximab, and 11 of 17 patients (65%) anakinra. After etanercept failure, drug survival of anakinra (65% on drug after 12 months, 95% CI 42-87%) was longer than of a second TNF-alpha antagonist for systemic JIA (21%, 95% CI 0-43%, log-rank p=0.006). Drug survival of anakinra as second/third agents was not different from drug survival of etanercept as first agent. (Figure 2B)

2A. NON-SYSTEMIC JIA

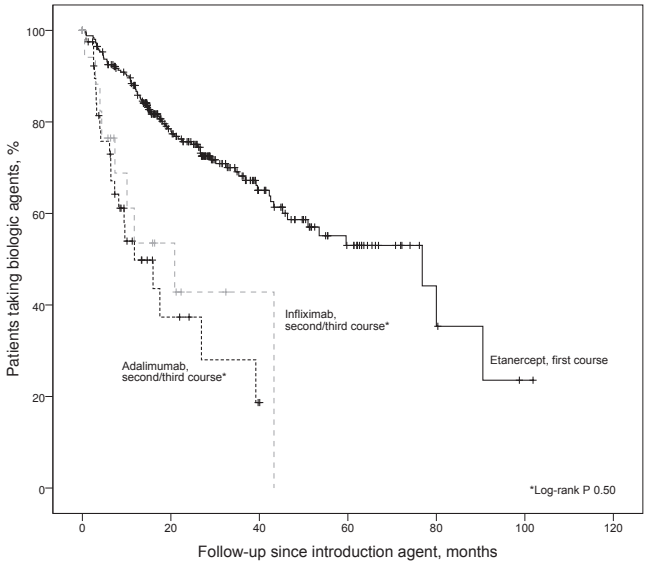

Table accompanying figure 2A:

	N of patients	N of patients with events	N of patients censored
Etanercept (first)	256	79	177
Adalimumab (second/third)	42	21	21
Infliximab (second/third)	21	9	12

Effectiveness of second biologic on active arthritis

Forty-five of the 59 patients that switched to a second agent due to ineffectiveness or loss of response had follow-up data 3 months after switch, and 2 of these 45 patients (4%) achieved inactive disease. Of the 43 patients with 15 months of follow-up, 5 patients (12%) achieved inactive disease.

Influence of reason switching

Patients who switched because of primary ineffectiveness to treatment (n=24, 2 patients excluded because of inclusion in drug trial) seemed to continue the second agent less often (32% on drug after 12 months, 95% CI 12-53%), than patients who switched because of loss of response (50% on drug after 12 months, 95% CI 30-70%), and the remaining reasons combined (61% on drug after 12 months, 95% CI 38-83%).

Discontinuation of a second biologic agent because of ineffectiveness was associated with ineffectiveness as reason to switch from the first to the second agent (OR 8.0, 95% CI 1.7-37.4), but not with adverse events as reason to switch from the first to the second biologic (OR 0.1, 95% CI 0.0-1.1).

2B. SYSTEMIC JIA

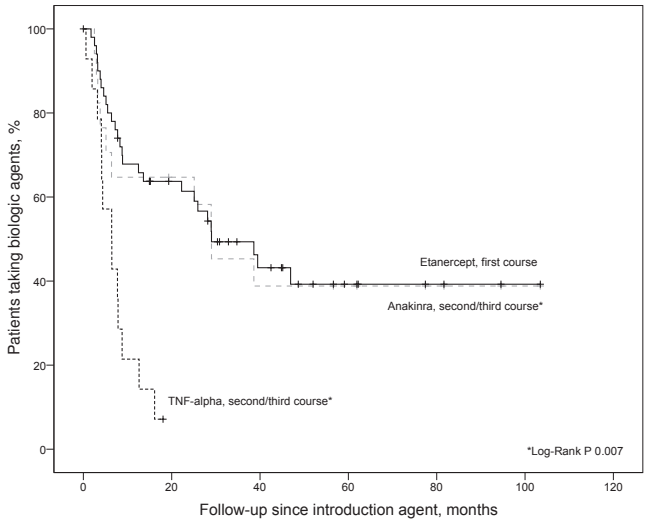

Table accompanying figure 2B:

	N of patients	N of patients with events	N of patients censored
Etanercept (first)	51	27	24
Anakinra (second/third)	17	10	7
Adalimumab or infliximab (second/third)	14	13	1

FIGURE 2 (A & B). Drug continuation of biological agents introduced in non-systemic and systemic JIA
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).
Figure 2A compares the drug survival of etanercept (introduced as first biological agent) with adalimumab and infliximab as second/third introduced agents for patients with non-systemic JIA categories. Figure 2B compares the drug survival of etanercept (introduced as first biological agent) with adalimumab and infliximab as second/third introduced agents for patients with systemic JIA. Log-rank test compares the drug survival difference between the second/third introduced biological gents (*-marked categories).

Of the 8 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; 4 patients (50%) discontinued treatment (2 because of a flare of arthritis, 1 because of adverse events and 1 reason unknown).

Safety of switching

Within 1 year after start of etanercept as first biologic, 0.23 AEs/patient-year and 0.01 SAEs/patient-year (0.55 AEs/patient-year of patients that switched) were reported, and within 1 year after start of the second biologic 0.32 AEs/patient-year and 0.00 SAEs/patient-year, and of the third biologic 0.36 AEs/patient-year and 0.00 SAEs/patient-year. Within the first year, 0.42 AEs/patient-year during the 49 adalimumab courses were observed, 0.19 AEs/patient-year during the 28 infliximab courses, and 0.32 AEs/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 biologic agent in JIA occurs frequently in daily practice and seems to be a safe option for JIA patients who failed etanercept. The effectiveness of a second (and third) biologic agent is debatable and seems especially low when the first biologic agent was discontinued because of primary ineffectiveness.

This is the second observational study on the effectiveness and safety of switching between biologic agents in JIA. In the present study, most patients switched from etanercept to adalimumab, while in the study by Tynjala et al. mainly a switch between etanercept and infliximab was described.[1] We showed that, while the drug survival of etanercept was significantly higher, 47% of the switchers, who previously did not responded to etanercept, continued their second biologic after 12 months of treatment. A lower percentage (32%) was seen for patients that discontinued etanercept because of primary ineffectiveness. This drug survival rate of a second biologic is slightly lower than the by Tynjala et al. reported 58%.[1] The number of patients that achieved inactive disease 15 months after switch (12%) was substantially lower than the reported 32% in previously biologically-naïve JIA patients treated with etanercept.[3] In RA, a meta-analysis with over 4,000 RA patients has been conducted and the drug survival of 61.8% 1 year after introduction of a second TNF-alpha antagonist of treatment seemed longer than in JIA.[19] In this 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 biologic agents was more effective, switching seems justifiable, since only very limited other therapeutic options are available after biologic treatment.

The question remains: "Which patients should switch and to which type of biologic?" We have shown that, in daily practice, patients with non-systemic JIA categories mainly

switched between TNF-alpha inhibitors only. An important observation was that, for patients with non-systemic JIA categories, no differences between effectiveness of adalimumab versus infliximab after etanercept failure were seen. Abatacept, even though it has been approved after TNF-alpha failure, was only used in 4 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. Nowadays, anakinra has a more prominent place in the treatment of systemic JIA with systemic features and is often the first choice biologic.[15] Other IL-1 and IL-6 antagonists were, besides prescriptions in the presence of randomized clinical trials, not available during this study period and therefore not observed in the present study.
Another observation was that patients who switched to a second biologic with uveitis as reason, all switched to adalimumab. Recently a study by Simonini et al. showed that adalimumab seems to be more efficacious in maintaining uveitis remission than infliximab.[20] Unfortunately the evaluation of the effectiveness on uveitis is beyond the scope of our register. However, we noticed that approximately half of the patients with uveitis needed to discontinue adalimumab because of a flare of the arthritis or intolerance.

In this study we showed that the AE rates are comparable for each course of biologic agents, and are also comparable for each specific biologic. This is in contrast with data from Curtis et al., who showed a higher rate of hospitalized infections in switchers compared with RA patients that did not switch and a higher rate of hospitalized infections with infliximab use compared with the use of other available biologics.[21] Furthermore we showed that adverse events as reason to switch from a first to a second agent did not influence the chance of discontinuation of the second agent for adverse events, however, the number of patients with adverse events is small. Our finding that switching between biologic 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 and differences in treatment strategies are known to exist. The observed switching patterns are inevitable influenced by the availability of biologic agents within the study period. The register started when etanercept became available for the treatment of JIA, and other biologics were introduced later, which will have had an effect on the treatment choices of physicians. Furthermore, the study period is limited till the patients become 18 years of age. For patients with a longer follow-up duration after start of etanercept we had a higher chance to observe a switch. The percentage of switching in this observational study is therefore likely to be underreported.

Therefore, together with the low number of patients per biologic treated, these indirect comparisons between the different biologics are difficult and could be biased.
Another limitation in this study is that the wash-out period of the first drug for evaluation of the second was not taken into account. Most patients switched to the second agent without a treatment pause. However, because the half life of etanercept is approximately 70 hours, the outcomes 3 months after switch are unlikely to be subject to a carry-over effect.
The switchers represent a heterogeneous patient group. The presence of systemic features, uveitis and anti-drug antibodies are all important factors which influences 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 biologic agent occurs frequently in daily practice and, since limited options are available, seems justifiable for JIA patients who failed 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 TNF-alpha blocking agent in systemic JIA. The effectiveness of a second biologic agent was lower than the first biologic and seems especially low when the first agent was discontinued because of primary ineffectiveness. Therefore, choosing the right first biologic agent is important.

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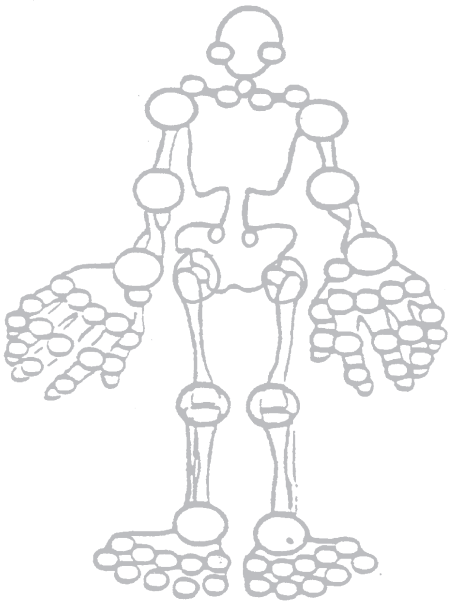
CHAPTER 5

Trends in prescription of biologic treatment in JIA

CHAPTER 5.1

Are changing prescription patterns of biologics for JIA associated with better patient' outcomes?



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Ready for submission:
Marieke H. Otten, Janneke Anink, Femke H.M. Prince, et al. Are changing prescription patterns of biologics for Juvenile Idiopathic Arthritis associated with better patient' outcomes?

ABSTRACT

Objective: To evaluate trends in prescription of biologic agents and influence on outcomes of JIA patients.

Methods: The ABC register (multicenter prospective observational study) aims to include all JIA patients in the Netherlands who use or used biologic agents since 1999. Patients were divided in time periods according to year of introduction of first biologic agent. Trends in characteristics of patients before introduction of first biologic and effectiveness of the first biologic were analyzed over 12 years.

Results: 343 non-systemic and 86 systemic JIA patients started at least 1 biologic agent between 1999 and 2010. Etanercept remained biologic of first choice for non-systemic JIA and anakinra has become first choice for systemic JIA. The use of systemic prednisone and synthetic disease-modifying anti-rheumatic drugs (besides methotrexate) prior to biologics decreased. During these 12 years of observation, biologics were prescribed after shorter disease durations and in patients with less baseline disease activity with regard to number of joints with arthritis and limited motion and functional disability scores. For systemic JIA, prescription patterns changed towards introduction in patients with higher ESR values and after as early as a median of 0.4 years of disease duration. These changes for both systemic and non-systemic JIA resulted in more patients with inactive disease and less joints with limited motion after 3 and 15 months of treatment.

Conclusions: Biologics are prescribed increasingly, earlier during the disease course and in JIA patients with lower disease activity. These changes are subsequently accompanied by better short-term disease outcomes. Etanercept remains biologic of first choice for non-systemic JIA and anakinra has become first choice for systemic JIA.

INTRODUCTION

Treatment of juvenile idiopathic arthritis (JIA) has changed dramatically since the introduction of biologic agents in 1999. Because of an increasing insight in the immunological and biologic pathways involved in the development of arthritis, the number of available biologic agents increased. Biologic agents targeting other cytokines than Tumour Necrosis Factor (TNF)-alpha, like interleukin (IL)-1 and IL-6, have become available. Together with the introduction of these new drugs, new insights in the treatment of JIA indicate that earlier and more aggressive therapy is associated with better outcomes.[1-3] While in the early nineties aggressive treatment was mainly applied when radiological damage was present, synthetic Disease Modifying Anti-Rheumatic Drugs (sDMARDs) and biologic agents are nowadays prescribed in order to prevent this damage.

Whether these new insights with regard to biologic treatment have been adopted in daily practice for JIA patients and resulted in better patient' outcomes is, to the best of our knowledge, still unknown.

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

PATIENTS AND METHODS

Study design and subjects

The Arthritis and Biologics in Children (ABC) register is a multicenter prospective observational study that aims to include all JIA patients in The Netherlands who use or previously used biologic agents. This register has been founded in 2003 and includes prospectively collected data since 1999, and data collection is still ongoing. 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. In the register, patient and disease characteristics are collected at baseline followed by data collection after 3 months of treatment and yearly thereafter. This includes, amongst others, the variables of the JIA disease activity score (i.e. 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 collecting follow-up data at 3 months and then yearly, extra data entry times were at the time of any important events including, when biologics were discontinued, type of biologic switched or when there were safety concerns.

To investigate time trends, patients were divided in time periods according to the year of introduction of first biologic agent. This analysis was limited to previous biologically-naïve patients who had started their first biologic agent. Switches to other agents were not taken into account. Results of the years 1999 and 2000 were combined, because the first biologic agent (etanercept) became available during the year 1999 and reimbursement started in 2000. Since systemic JIA is currently considered as a different disease entity because of different clinical presentation, pathophysiology and response to treatment, results for the systemic JIA patients and the patients with non-systemic JIA categories (i.e. all JIA categories besides systemic JIA) were presented separately.

Statistical analysis

Descriptive statistics were reported as absolute frequencies, or as median values with an interquartile range (IQR). For each year the percentage of patients with disease duration below the lower quartile and above the upper quartile of the total systemic and non-systemic population were calculated.

Treatment effect was evaluated using drug survival and the number of patients meeting the definition of inactive disease. The one-year and two-year drug survival (i.e. percentage of patients that still receive the biologic agent after one and two years respectively, censored for the time a patient discontinued because of remission or, if still on the drug, at last follow-up moment) were estimated with the use of Kaplan-Meier analysis. Inactive disease was 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).[4] To account for patients who had withdrawn from treatment, the LUNDEX-corrected inactive disease was calculated by multiplying the fraction of patients still on the drug after 3 and 15 months with the proportion of patients with inactive disease after 3 and 15 months respectively.[5]

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 in a Cox proportional Hazards model with year of start as covariate.

A second analysis was conducted to identify homogeneous clusters of patients with regard to values of the JIA core set variables at time of introduction of first biologic agent. The two-step auto-cluster procedure developed by SPSS was used to identify the optimal number of clusters on the basis of the Akaike Information Criterion (AIC, a measurement of goodness of fit) together with the distance change. The ANOVA indicated

which variable contributed the most. After defining these clusters, the patients within the different clusters were compared with regard to additional baseline characteristics and treatment outcomes.

Missing were: 12.2% of variables (including VAS pain) of the JIA core sets at observed follow-up moments (start of treatment, after 3 and 15 months) with a median of 0 variables per core set. If a minimum of 3 (of the 7) variables per core set was present, the remaining variables were imputed with the use of the multiple imputation method of the AregImpute function of the *R* statistical package (imputation occurred in 8.4% of variables). All reported p-values were based on 2-sided tests for significance, and p-values <0.05 were considered statistically significant. SPSS version 17.0.1 and *R* statistical package 2.12.1 were used for the analyses.

RESULTS

A total of 343 non-systemic JIA patients and 86 systemic JIA patients started their first biologic agent between 1999 and 2010. The number of biologically-naïve JIA patients that initiated a biologic agent increased from 12 in 1999-2000 to 82 in 2010, which is illustrated in Figure 1. During these 12 years of observation, the JIA population taken into consideration to initiate biologic treatment has changed.

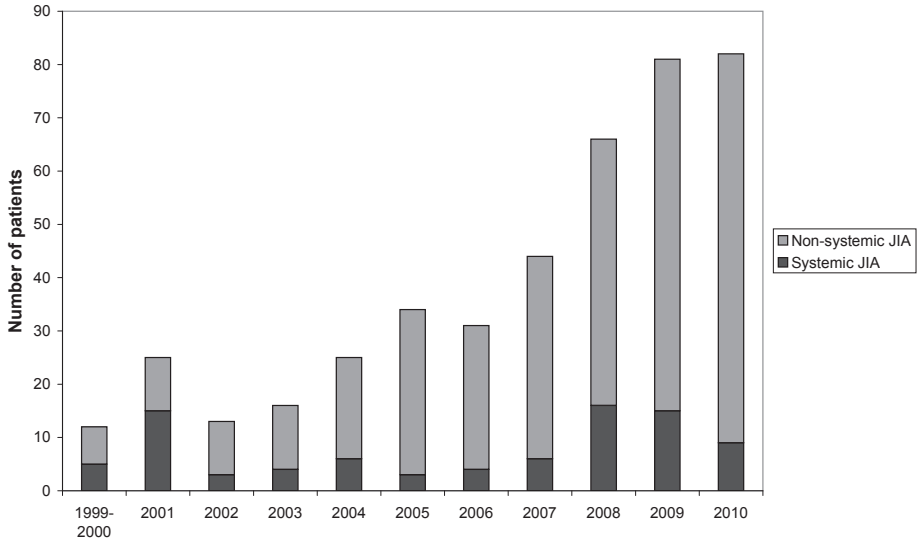

FIGURE 1. Number of biologically-naive non-systemic and systemic JIA patients considered for biologic treatment between 1999 and 2010

TABLE 1. Characteristics and outcomes of non-systemic JIA patients between 1999 and 2010

	1999-2000 N=7	2001 N=10	2002 N=10	2003 N=12	2004 N=19
Patient characteristics at baseline					
Female	6 (86)	9 (90)	9 (90)	9 (75)	12 (63)
Age onset JIA, median (IQR), y	4.1 (1.6-8.0)	2.9 (2.1-6.3)	6.5 (3.2-9.3)	8.5 (3.4-12.0)	8.9 (5.6-9.9)
Disease duration before start, median (IQR), y	5.3 (3.9-8.1)	8.5 (6.3-12.6)	3.8 (2.2-8.0)	3.1 (0.9-8.6)	3.3 (2.1-6.0)
Disease duration < first quartile (1.5y)	0 (0)	0 (0)	1 (10)	4 (33)	2 (11)
Disease duration > third quartile (6.7y)	3 (43)	7 (70)	3 (30)	4 (33)	4 (21)
JIA category					
Poly-articular JIA RF+	3 (43)	-	1 (10)	1 (8)	3 (16)
Poly-articular JIA RF-	1 (14)	8 (80)	6 (60)	8 (67)	10 (53)
Oligo-articular extended	2 (29)	2 (20)	1 (10)	2 (17)	3 (16)
Oligo-articular persist	-	-	-	-	-
Psoriatic Arthritis	-	-	2 (20)	-	2 (11)
ERA	1 (14)	-	-	1 (8)	1 (5)
Undifferentiated arthritis	-	-	-	-	-
Medication history before start first biologic					
Systemic steroid use	6 (86)	7 (70)	7 (70)	4 (33)	7 (37)
Methotrexate use	7 (100)	10 (100)	10 (100)	12 (100)	18 (95)
Other sDMARD use (beside methotrexate)	7 (100)	7 (70)	8 (80)	7 (58)	7 (37)
First biologic agent started					
Etanercept	7 (100)	10 (100)	9 (90)	12 (100)	19 (100)
Adalimumab	-	-	-	-	-
Infliximab	-		1 (10)	-	-
Disease activity at baseline					
VAS physician, median (IQR)	74 (22-77)	79 (62-87)	76 (53-81)	76 (50-83)	68 (57-73)
No. of active joints, median (IQR)	11 (6-14)	20 (18-37)	19 (9-23)	13 (6-27)	9 (7-16)
No. of limited joints, median (IQR)	7 (4-8)	15 (11-21)	11 (7-15)	9 (3-18)	6 (4-12)
CHAQ score, median (IQR)	2.0 (1.0-2.0)	1.5 (1.2-2.6)	2.3 (1.4-2.7)	1.8 (0.5-2.1)	1.5 (1.0-2.4)
VAS pain, median (IQR)	45 (27-65)	71 (23-75)	75 (36-89)	32 (11-49)	65 (22-71)
VAS wellbeing, median (IQR)	35 (27-60)	70 (27-75)	53 (34-77)	49 (22-73)	58 (27-82)

2005 N=31	2006 N=27	2007 N=38	2008 N=50	2009 N=66	2010 N=73	P for trend
25 (81)	20 (74)	28 (74)	34 (68)	42 (64)	49 (67)	0.02
8.1 (3.9-11.0)	7.2 (3.1-11.5)	8.6 (4.4-12.6)	10.3 (6.3-12.2)	7.7 (2.4-12.3)	7.2 (2.3-10.8)	0.64
3.0 (1.5-6.0)	4.5 (1.7-8.5)	2.7 (1.1-2.7)	1.9 (1.3-3.2)	2.9 (1.2-6.0)	3.0 (1.1-6.5)	0.005
8 (26)	4 (15)	10 (26)	18 (36)	21 (32)	20 (27)	0.005
7 (23)	9 (33)	10 (26)	5 (10)	16 (24)	18 (26)	0.02
4 (13)	2 (7)	2 (5)	6 (12)	7 (11)	7 (10)	-
11 (36)	12 (44)	18 (47)	22 (44)	31 (47)	25 (34)	-
11 (36)	9 (33)	11 (29)	12 (24)	12 (18)	16 (22)	-
-	-	1 (3)	3 (6)	10 (15)	8 (11)	-
4 (13)	2 (7)	3 (8)	5 (10)	2 (3)	6 (8)	-
1 (3)	2 (7)	3 (8)	2 (4)	4 (6)	10 (14)	-
-	-	-	-	-	1 (2)	-
16 (52)	13 (48)	11 (29)	22 (44)	25 (38)	26 (36)	0.004
31 (100)	27 (100)	36 (95)	50 (100)	66 (100)	73 (100)	0.46
14 (45)	17 (63)	18 (47)	20 (40)	19 (29)	22 (30)	<0.001
31 (100)	26 (96)	36 (95)	47 (94)	59 (89)	60 (82)	-
-	1 (4)	-	1 (2)	7 (11)	12 (16)	-
-	-	2 (5)	2 (4)	-	1 (1)	-
64 (54-79)	60 (40-71)	53 (40-70)	60 (40-70)	50 (39-69)	40 (20-59)	<0.001
11 (7-24)	10 (6-18)	9 (6-16)	8 (5-16)	6 (3-8)	4 (2-7)	<0.001
7 (5-13)	10 (5-14)	5 (3-16)	4 (2-10)	3 (2-7)	3 (1-4)	<0.001
2.0 (1.1-2.4)	1.5 (1.0-2.0)	1.4 (1.0-2.0)	1.4 (0.9-2.0)	1.0 (0.4-1.6)	0.9 (0.3-1.6)	<0.001
60 (30-82)	55 (37-74)	62 (43-73)	61 (34-75)	43 (17-75)	48 (16-65)	0.02
61 (34-80)	49 (25-70)	65 (46-76)	56 (37-75)	43 (15-64)	40 (14-70)	0.001

	1999-2000 N=7	2001 N=10	2002 N=10	2003 N=12	2004 N=19
Disease activity at baseline (continued)					
ESR, median (IQR), mm/h	16 (8-45)	24 (13-36)	27 (13-39)	27 (15-30)	16 (10-38)
Disease activity after 3 months treatment†	*N=6*	*N=10*	*N=9*	*N=10*	*N=19*
VAS physician, median (IQR)	15 (9-15)	17 (11-30)	12 (4-47)	23 (17-43)	10 (5-15)
No. of active joints, median (IQR)	3 (0-9)	4 (3-9)	4 (1-8)	3 (2-9)	1 (0-2)
No. of limited joints, median (IQR)	5 (2-8)	7 (2-17)	2 (1-11)	3 (1-10)	5 (1-9)
CHAQ score, median (IQR)	0.5 (0.3-1.6)	1.0 (0.6-1.5)	1.4 (0.4-1.8)	0.9 (0.4-1.8)	0.6 (0-1.0)
VAS pain, median (IQR)	3 (2-20)	6 (0-54)	19 (7-61)	14 (4-53)	10 (5-15)
VAS wellbeing, median (IQR)	3 (0-37)	11 (2-33)	24 (3-67)	22 (3-59)	8 (2-12)
ESR, median (IQR), mm/h	11 (8-18)	14 (4-25)	12 (5-24)	19 (9-33)	5 (4-11)
Inactive Disease	0 (0)	1 (10)	2 (22)	0 (0)	5 (26)
LUNDEX- Inactive Disease, %	0	8	22	0	26
Disease activity after 15 months treatment†	*N=6*	*N=9*	*N=6*	*N=9*	*N=18*
VAS physician, median (IQR)	8 (0-14)	12 (2-43)	8 (4-25)	25 (5-33)	3 (0-11)
No. of active joints, median (IQR)	1 (0-5)	2 (1-15)	2 (0-8)	2 (1-5)	0 (0-1)
No. of limited joints, median (IQR)	6 (2-8)	7 (2-17)	5 (2-9)	1 (0-5)	2 (0-4)
CHAQ score, median (IQR)	0.4 (0-1.8)	1.1 (0.4-1.6)	0.2 (0-1.7)	0.9 (0.5-1.9)	0.2 (0-0.8)
VAS pain, median (IQR)	2 (1-23)	4 (3-46)	3 (0-34)	20 (2-77)	1 (0-9)
VAS wellbeing, median (IQR)	18 (1-41)	17 (2-70)	10 (3-35)	30 (3-70)	1 (0-9)
ESR, median (IQR), mm/h	10 (8-31)	9 (3-23)	7 (5-19)	10 (3-31)	5 (3-20)
Inactive Disease	2 (33)	1 (11)	3 (50)	1 (11)	9 (50)
LUNDEX- Inactive Disease, %	25	8	43	8	44
Drug survival (Kaplan-Meier)					
% of patients on drug after 1 year	100	100	90	92	95
% of patients on drug after 2 years	83	100	54	75	90

Numbers given are, if not stated differently, numbers of patients (%)

† Given are the number of patients with follow-up measurements after 3 and 15 months respectively.

[JIA= juvenile idiopathic arthritis; IQR=interquartile range; RF=rheumatoid factor; ERA=enthesitis related arthritis; DMARD=disease modifying drug; VAS=visual analogue scale; CHAQ= childhood health questionnaire; ESR=erythrocyte sedimentation rate]

Non-systemic JIA categories

The patient' characteristics and outcomes for each year patients with non-systemic JIA categories started a biologic agent are reported in Table 1. In 2010, the majority (82%) of patients initiated etanercept as first choice, against 16% of patients that started adalimumab. In the first 5 years, mainly patients with poly-articular (rheumatoid factor positive and negative) and oligo-articular extended categories started biologics, and during more recent years, more patients with the oligo-articular persistent subtype, psoriatic

2005 N=31	2006 N=27	2007 N=38	2008 N=50	2009 N=66	2010 N=73	P for trend
21 (10-36)	21 (11-40)	12 (6-28)	12 (6-34)	11 (6-25)	10 (5-24)	<0.001
N=31	*N=26*	*N=36*	*N=43*	*N=60*	*N=61*	
12 (1-20)	14 (8-21)	10 (6-20)	23 (10-40)	13 (5-35)	10 (1-24)	0.24
2 (0-4)	2 (0-6)	1 (0-4)	2 (0-8)	1 (0-5)	0 (0-2)	<0.001
3 (1-5)	4 (1-8)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	<0.001
0.7 (0-1.5)	0.8 (0.1-1.0)	0.8 (0.3-1.0)	0.6 (0.1-1.4)	0.4 (0.1-1.3)	0.6 (0.2-1.1)	0.03
8 (0-26)	20 (7-43)	20 (10-40)	31 (3-60)	15 (4-49)	10 (2-40)	0.57
10 (0-39)	15 (5-32)	19 (12-35)	28 (4-54)	16 (2-44)	11 (2-47)	0.25
8 (3-17)	9 (6-12)	8 (3-13)	6 (2-11)	6 (4-11)	7 (3-15)	0.01
7 (23)	6 (23)	11 (31)	7 (16)	18 (30)	22 (36)	0.01
21	22	29	15	30	34	0.01
N=25	*N=21*	*N=31*	*N=35*	*N=51*	-	
3 (0-23)	8 (0-25)	6 (0-25)	10 (4-35)	1 (0-21)	-	0.31
0 (0-2)	0 (0-3)	0 (0-2)	1 (0-5)	0 (0-3)	-	0.06
1 (0-4)	2 (0-4)	0 (0-2)	1 (0-2)	1 (0-2)	-	0.001
0.3 (0-1.0)	0.9 (0-1.1)	0.4 (0.1-0.9)	0.3 (0-1.3)	0.3 (0-1.3)	-	0.14
2 (0-23)	14 (1-50)	20 (0-40)	21 (0-60)	3 (0-436)	-	0.90
0 (0-12)	9 (1-39)	13 (3-32)	20 (0-45)	4 (0-36)	-	0.57
8 (6-17)	7 (4-12)	5 (5-9)	7 (4-14)	5 (3-9)	-	<0.001
10 (32)	11 (52)	15 (48)	11 (31)	29 (57)	-	0.02
27	38	37	22	49	-	0.02
87	89	79	81	89	85	0.16
79	71	73	68	71	NA	0.20

arthritis and enthesitis related arthritis were considered. The first biologic was initiated after a median disease duration of 3.0 (IQR 1.5-6.7) years for all non-systemic JIA patients combined. The proportion of patients with less than 1.5 years of disease duration before start of the first biologic agent increased from zero in the years 1999-2001 to 31% in 2008-2010. Furthermore, the use of systemic corticosteroids decreased (77% in 1999-2001 to 39% in 2008-2010), as well as the use of other sDMARDs besides methotrexate (82% in 1999-2001 to 32% in 2008-2010).

At start of the first biologic, a less severe disease activity is observed nowadays with, amongst others, less joints with active arthritis (median of 18 joints in 1999-2001 decreased to 5 joints in 2008-2010), less joints with limited motion (median of 12 joints in

TABLE 2. Cluster analysis of non-systemic JIA patients

	Cluster*		
	1	2	
	N=179	N=156	p-value†
Variables of the JIA core set at baseline			
Physicians' global, mean (95% CI), range 0-100	42 (39-45)	66 (63-68)	<0.001
CHAQ score, mean (95% CI), range 0-3	0.9 (0.8-1.0)	1.9 (1.8-2.0)	<0.001
VAS pain, mean (95% CI), range 0-100	33 (29-36)	70 (67-73)	<0.001
VAS wellbeing, mean (95% CI), range 0-100	33 (29-37)	68 (64-71)	<0.001
Number of joints with active arthritis, mean (95% CI)	6 (5-6)	16 (14-18)	<0.001
Number of joints with limited motion, mean (95% CI)	4 (3-4)	11 (10-13)	<0.001
ESR, mean (95% CI), mm/h	17 (15-19)	26 (22-29)	<0.001
Additional characteristics and measurements			
Female (n=237)	121 (68)	116 (74)	0.18
Median year at start first biologic	2009	2007	<0.001
Subtype JIA			
Poly-articular JIA RF- (n=150)	64 (36)	86 (55)	<0.001
Poly-articular JIA RF+ (n=36)	15 (8)	21 (13)	0.13
Oligo-articular extended (n=81)	50 (28)	31 (20)	0.09
Oligo-articular persistent (n=20)	19 (11)	1 (1)	<0.001
Psoriatic Arthritis (n=24)	15 (8)	9 (6)	0.36
ERA (n=23)	15 (8)	8 (5)	0.24
Undifferentiated (n=1)	1 (1)	0 (0)	-
Disease duration before start, median (IQR), y	3.3 (1.5-6.9)	2.5 (1.5-6.7)	0.15
No. of patients with disease duration before start <2yrs (n=119)	58 (32)	61 (39)	0.20
No. of patients with disease duration before start <5yrs (n=226)	118 (66)	108 (69)	0.42
No. of patients with inactive disease after 3 months (n=77 of 309 patients with measurement at 3 months)	50 (31)	27 (18)	0.02
No. of patients with inactive disease after 15 months (n=103 of 239 patients with measurement at 3 months)	64 (52)	39 (34)	0.003
% of patients on drug after 1 year (95% CI)	91 (87-96)	83 (77-89)	0.03
% of patients on drug after 2 year (95% CI)	80 (73-87)	71 (63-79)	0.07

* 8 patients had to be excluded because of outlying or missing values

† p-values on the basis of ANOVA (mean continuous variables of JIA core set), Mann-Whitney-U test (median continuous variables), Pearson Chi-Square test (categorical variables) or Cox regression model (drug survival data)

On the basis of the JIA core set variables before start first biologic 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 2 cluster groups on the basis of AIC and the ratio of distance measures. The ANOVA indicated which variable contributed the most: Physicians' global (*F* 123.749), CHAQ score (*F* 210.333), VAS pain (*F* 240.840), VAS wellbeing (*F* 179.850), number of joints with arthritis (*F* 139.281) and number of joints with limited motion (*F* 119.740), and ESR (*F* 17.669). (Variables with large *F* values provide the greatest separation between clusters).

Overall, patients classified in Cluster 1 continued the drug for a median of 77 (95% CI 34-120) months compared with patients in Cluster 2 for a median of 54 (95% CI 34-73) months (Log-rank: p=0.048).

1999-2001 decreased to 3 joints in 2008-2010) and lower CHAQ scores (median score of 1.8 in 1999-2001 decreased to 1.1 in 2008-2010). Between 1999 and 2010, more patients achieved inactive disease after 3 months and 15 months of treatment. Drug survival after one and two years of treatment was not affected by these changes. Furthermore, a trend was observed towards fewer joints with limited motion after 3 months and 15 months of treatment.

In a cluster analysis, more homogeneous groups of non-systemic JIA patients were identified based on the core set variables before introduction of first biologic agents. The patient and disease characteristics of these 2 clusters of patients are presented in Table 2. Cluster 1 (n=179) represents the less severely affected patients at baseline and cluster 2 (n=156 patients) the more severely affected patients. Patients classified in cluster 2 started biologic agents during earlier years (median year of start first biologic 2007) compared with patients in cluster 1 (2009). The disease duration before start of first biologic agent was not different between clusters. Patients who were more severely affected at baseline achieved less often inactive disease and discontinued the first agent more often because of ineffectiveness or intolerance.

Systemic JIA

The characteristics and outcomes of systemic JIA patients who started a biologic agent between 1999 and 2010 are reported in Table 3. Because of low numbers of systemic JIA patients that started biologic treatment each year, the results are presented in 4 time periods. Until 2007 etanercept was prescribed most often in systemic JIA. In 2008 anakinra has become first biologic treatment choice. Since 2008, biologic treatment was also started earlier (after median of 0.4 years of disease duration), and in some patients even before the use of steroids and sDMARDs. Furthermore, the number of active joints with arthritis decrease from 18 to 3 joints, and the number of limited joints with arthritis decreased from 12 to 2 joints in 2010. In contrast to the non-systemic categories, no differences in the subjective measurements for pain and wellbeing by patient or parents and a significant increase in ESR values were seen over time. After 3 months of treatment all variables of the JIA core set, including the patient/parents measurements and ESR values, decreased significantly. Most outstanding is the change in CHAQ score, from a median of 1.9 points in the years 1999-2001 to 0.4 points in 2008-2010. As in the non-systemic JIA group, more patients achieved inactive disease after 3 and 15 months of treatment during the more recent years. Drug survival was not affected by these changes.

In a cluster analysis, 3 clusters of systemic JIA patients were identified. The patient and disease characteristics of the patients classified in these clusters are presented in Table 4. Patients in cluster 3 appeared to be the most severely affected patients with high joint counts with arthritis and limited motion. These patients were treated during the

TABLE 3. Characteristics and outcomes of patients with systemic JIA between 1999 and 2010

	1999-2001 N=20	2002- 2004 N=13	2005-2007 N=13	2008-2010 N=40*	P for trend
Patient characteristics at baseline					
Female	10 (50)	8 (62)	10 (77)	17 (43)	0.65
Age onset JIA, median (IQR), y	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), y	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
Disease duration < first quartile (0.3y)	1 (5)	1 (8)	0 (0)	19 (48)	<0.001
Disease duration > third quartile (4.0y)	7 (35)	4 (31)	5 (39)	5 (13)	0.01
Medication history before introduction of first biologic agent					
Systemic steroid use	18 (90)	13 (100)	13 (100)	20 (50)	<0.001
Methotrexate use	19 (95)	13 (100)	13 (100)	24 (60)	0.001
Other sDMARD use (besides methotrexate)	6 (30)	3 (23)	4 (31)	3 (8)	0.02
First biologic agent started					
Etanercept	18 (90)	13 (100)	11 (84)	11 (28)	-
Anakinra	-	-	2 (15)	29 (73)	-
Infliximab	2 (10)	-	-	-	-
Disease activity at baseline					
VAS physician, median (IQR)	72 (52-82)	69 (57-72)	63 (36-84)	40 (29-53)	<0.001
No. of active joints, median (IQR)	18 (9-26)	13 (8-20)	6 (4-10)	3 (2-5)	<0.001
No. 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
Disease activity after 3 months treatment†	*N=18*	*N=12*	*N=12*	*N=38*	
VAS physician, median (IQR)	36 (17-55)	14 (10-78)	18 (10-35)	0 (0-18)	<0.001
No. of active joints, median (IQR)	5 (1-20)	3 (0-25)	2 (0-9)	0 (0-0)	<0.001
No. of limited joints, median (IQR)	8 (6-15)	6 (2-17)	6 (1-10)	0 (0-2)	<0.001
CHAQ score, median (IQR)	1.9 (0.9-2.3)	1.7 (0.8-2.5)	0.9 (0.5-2.3)	0.4 (0-0.9)	<0.001
VAS pain, median (IQR)	43 (16-59)	17 (1-79)	18 (4-37)	1 (0-21)	<0.001
VAS wellbeing, median (IQR)	46 (7-58)	9 (1-61)	15 (5-38)	4 (0-26)	0.001
ESR, median (IQR), mm/h	34 (7-86)	20 (12-45)	18 (13-23)	8 (4-16)	<0.001
Inactive Disease	0 (0)	2 (17)	1 (8)	25 (66)	<0.001
LUNDEX-Inactive Disease, %	0	17	7	64	<0.001

	1999-2001 N=20	2002- 2004 N=13	2005-2007 N=13	2008-2010 N=40*	P for trend
Disease activity after 15 months treatment†	*N=13*	*N=11*	*N=9*	*N=37*	
VAS physician, median (IQR)	16 (5-34)	3 (0-43)	10 (0-12)	0 (0-09)	0.003
No. of active joints, median (IQR)	1 (1-5)	0 (0-3)	0 (0-2)	0 (0-1)	0.01
No. of limited joints, median (IQR)	8 (5-10)	3 (0-10)	0 (0-2)	0 (0-2)	<0.001
CHAQ score, median (IQR)	0.9 (0.3-2.2)	0.8 (0-2.2)	0.4 (0-0.9)	0.1 (0-0.6)	0.003
VAS pain, median (IQR)	15 (0-43)	10 (3-33)	10 (0-36)	3 (0-10)	0.08
VAS wellbeing, median (IQR)	25 (2-46)	5 (2-25)	5 (0-33)	3 (0-15)	0.04
ESR, median (IQR), mm/h	13 (7-27)	5 (4-34)	11 (7-19)	11 (5-23)	0.47
Inactive Disease	2 (15)	6 (55)	2 (22)	22 (60)	0.02
LUNDEX-Inactive Disease, %	9	38	14	43	0.02
Drug survival (Kaplan-Meier)					
% of patients on drug after 1 year	60	69	66	76	0.14
% of patients on drug after 2 years	55	61	66	66	0.19

* One patient was previously diagnosed as systemic JIA in 2006, but diagnosis was changed to polyarticular course JIA in 2008. † Given are the number of patients with follow-up measurements after 3 and 15 months.

earlier years and seem to reflect the "former" systemic JIA population. The cluster 1 and 2 patients both started biologic treatment in 2008 and reflect the current JIA population. This population can be classified in 2 patient groups that are mainly separated by ESR values, CHAQ scores and assessment of disease activity by the physician and assessments of pain and wellbeing by the patient/parents. The patients with lower ESR values, lower CHAQ scores and lower assessments of disease activity, pain and wellbeing, achieved inactive disease more often. No differences in drug survival were found between cluster 1 and cluster 2 systemic JIA patients, but drug survival in cluster 3 was significantly lower.

DISCUSSION

This overview of 12 years of biologic treatment observation in The Netherlands allows us to conclude that biologics are being prescribed increasingly and the threshold to initiate biologics has been decreased towards shorter disease duration and lower disease activity.

Etanercept remains biologic of first choice for patients with non-systemic JIA categories, and anakinra has become first choice for systemic JIA. These changes in prescription behaviour of physicians are accompanied by better short-term disease outcomes.

TABLE 4. Cluster analysis of systemic JIA patients

	Cluster*			
	1	2	3	
	N=24	N=38	N=23	p-value†
Variables of the JIA core set at baseline				
Physicians' global, mean (95% CI), range 0-100	61 (52-71)	40 (33-47)	71 (65-77)	<0.001
CHAQ score, mean (95% CI), range 0-3	2.5 (2.3-2.6)	1.1 (0.8-1.3)	2.2 (2.0-2.4)	<0.001
VAS pain, mean (95% CI), range 0-100	80 (74-86)	40 (31-48)	57 (44-70)	<0.001
VAS wellbeing, mean (95% CI), range 0-100	80 (73-86)	39 (31-46)	45 (31-60)	<0.001
Number of joints with active arthritis, mean (95% CI)	6 (5-7)	5 (3-6)	22 (18-25)	<0.001
Number of joints with limited motion, mean (95% CI)	5 (3-7)	4 (3-6)	17 (13-21)	<0.001
ESR, mean (95% CI), mm/h	107 (95-119)	54 (40-69)	55 (39-70)	<0.001
Additional characteristics and measurements				
Female	13 (54)	17 (45)	11 (48)	0.77
Median year at start first biologic	2008	2008	2001	<0.001
Disease duration before start, median (IQR), y	0.5 (0.1-4.0)	1.3 (0.1-3.7)	2.4 (1.1-5.0)	0.04
% op patients on anakinra	14 (58)	15 (39)	2 (9)	0.002
No. of patients with disease duration before start <2yrs	17 (71)	24 (63)	10 (43)	0.14
No. of patients with disease duration before start <5yrs	20 (83)	32 (84)	17 (74)	0.58
No. of patients with inactive disease after 3 months (n=79 patients with measurement at 3 months)	9 (39)	18 (51)	1 (5)	0.002
No. of patients with inactive disease after 15 months (n=69 patients with measurement at 15 months)	8 (42)	17 (52)	7 (41)	0.71
% of patients on drug after 1 year (95% CI)	63 (41-85)	80 (67-93)	61 (41-81)	0.72 / 0.08**
% of patients on drug after 2 year (95% CI)	63 (41-85)	73 (57-88)	57 (36-77)	0.69 / 0.49**

* 1 patient had to be excluded because of outlying / missing values

† p-values on the basis of ANOVA (differences of mean values of JIA core set at baseline), Kruskal-Wallis test (non-parametric, continuous variables), Pearson Chi-Square test (non-parametric, categorical variables) or Cox regression model (drug survival analysis)

** Cluster 3 as reference: difference between cluster 1 and 3 (1 year survival p=0.72, 2 year survival p=0.69), and between cluster 2 and 3 (1 year survival p=0.08, 2 year survival p=0.49).

On the basis of the JIA core set variables before start first biologic 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 3 cluster groups on the basis of AIC and the ratio of distance measures. The ANOVA indicated which variable contributed the most: Physicians' global (*F* 19.782), CHAQ score (*F* 49.811), VAS pain (*F* 20.083), VAS wellbeing (*F* 20.461), number of joints with arthritis (*F* 92.654) and number of joints with limited motion (*F* 37.302), and ESR (*F* 16.530). (Variables with large *F* values provide the greatest separation between clusters).

Overall, patients classified in Cluster 1 continued the drug for a mean of 42 (95% CI 30-55) months compared with a mean of 54 (95% CI 42-65) months for cluster 2 patients and a mean of 37 (95% CI 21-53) months for cluster 3 patients (Log-rank (Mantel-Cox): p=0.025).

This is, to the best of our knowledge, the first study that describes trends in prescription patterns of biologic agents in JIA. An increasing trend in the prescription of biologics in JIA is observed. This increase is not likely to be influenced by an overall increase in the incidence of JIA, however, epidemiological data during the last decade are lacking. Peterson et al. reported in 1996 a decreasing incidence of juvenile rheumatoid arthritis (earlier terminology for JIA) during a 33-year observation period in Northern America, while no decline in incidence was found in a population-based study from Finland 1980-1990 and an increase between 1990 and 1995.[6-7]
Similar patterns in prescription of biologic 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.[8-11] One of these studies in RA found, similar to the present study in JIA, a decrease in disease duration before start biologic treatment.[9] It is likely that these observed changes during the last decade are also observed in patients that are considered for treatment with sDMARDs. The mind set of treating physicians has changed overall and transformed the care of JIA towards treating patients earlier and more aggressively.

Compared to non-systemic JIA, the prescription patterns for the systemic JIA population have changed even more strikingly and are most evident since 2008, when more scientific evidence indicated that anakinra seemed highly effective for the treatment of systemic JIA.[12-15] Timing of biologic treatment changed dramatically and biologics were introduced after a median of 0.4 years of disease duration and sometimes even before the use of systemic steroids and sDMARDs. While the number of joints with active arthritis, joints with limited motion and the total CHAQ scores decreased at baseline, the ESR levels increased. This might indicate that biologics are started at a more acute phase of the disease with more systemic features present. These patients are during such episodes with systemic features very ill in general, which is more pronounced than the burden of the arthritis. Therefore it is not surprisingly that the subjective measures of pain and wellbeing by the patient or parents at baseline did not change for systemic JIA patients taken into consideration for biologics during the last 12 years.

While biologic treatment was previously almost exclusively prescribed in order to treat the arthritis, currently these agents are also prescribed to control systemic features early during the disease course or uveitis. The majority of patients with non-systemic JIA remain treated with etanercept as first choice. Adalimumab was only prescribed in a subset of patients. It is likely that these patients had (a history of) uveitis, because adalimumab is now considered to be the preferred biologic treatment of childhood uveitis.[16-18] Systemic JIA patients are nowadays more often treated with IL-1 antagonists than TNF-alpha inhibitors. This change in prescribed biologics for systemic JIA was

expected, because increasing knowledge on the biologic and immunological pathways involved in the development of arthritis and associated systemic features resulted in a favour of IL-1 (and IL-6) antagonists.[19-20] The IL-6 inhibitor tocilizumab, though approved for active systemic JIA by the Food and Drug Administration (FDA) in April 2011, was not prescribed in The Netherlands outside the conducted clinical trials until 2010. It is likely that tocilizumab will be used increasingly in daily practice in the future, but its place in biologic treatment algorithms for systemic JIA still needs to be determined.

Together with the changes in prescription patterns, the treatment goal of inactive disease is achieved increasingly during the last 12 years for all JIA categories. Previous studies already indicated that earlier treatment with methotrexate, sulfasalazine or etanercept resulted in better outcomes and these indications are confirmed by this current study.[1-3, 21] Also for systemic JIA patients it has been demonstrated that anakinra is, if given as a first-line drug, highly effective on both systemic features and arthritis, and a reduced effect in long-standing systemic disease was found.[12, 22-23] Although more patients achieved inactive disease, drug survival did not change during the observed 12 years of treatment. Also in RA drug survival seems to be unaffected.[8-9] We expected that, because of better treatment responses, the drug survival would increase. However, this effect might have been equilibrated by the fact that, if treatment is not effective, treatment will be discontinued earlier, because more treatment options are available. Whether these observed trends also result in better outcomes for the long-term including the prevention of radiological damage is expected but needs to be elucidated. The achievement of inactive disease without any damage and functional limitations has to remain main treatment goal, however, treatment also needs to be weighted against the safety profiles which are for the long-term to a large extent still unknown.

In a secondary analysis, clusters of non-systemic and systemic JIA patients have been identified with regard to disease activity at baseline. These clusters reflect more homogenous groups of patients with regard to baseline disease activity and might provide the treating clinicians better insight in the consequences of treating patients with low disease activity. Non-systemic JIA patients with a high baseline disease activity achieved inactive disease less often and also discontinued the agents more often because of ineffectiveness or intolerance. Patients with systemic JIA have been clustered in 3 patient groups. The current systemic JIA population has been divided in more and less severely affected patients, however the differences are less pronounced. Unfortunately, presence of systemic features was not recorded in the register. More detailed evaluation of differences within the systemic category, including the influence of the presence of systemic features, and subsequently differences in treatment responses are needed.

The most severely affected systemic JIA patients seem to reflect the "former" population and these patients had worse outcomes. It is reassuring that these very severely affected systemic JIA patients have not been observed during recent years.

The present study shows that for non-systemic JIA patients, the ESR levels before introduction of biologic agents are nowadays found to be (for the larger extent) within the normal range. The function of ESR as variable of the JIA core set to evaluate treatment response in these patients might therefore be questioned as no further improvement from normal can be expected. In fact, because of a decreasing disease activity in all core set variables at baseline, the validity of the ACR paediatric response criteria that evaluates response as the percentage change in each variable of the JIA core set needs to be re-evaluated.[24]

This observational study has strengths but also some limitations. The ABC register includes almost all JIA patients that initiated biologic treatment in The Netherlands, with exclusion of patients enrolled in clinical trials. Therefore, the role of selection bias is negligible. However, if data is analyzed as a repeated cross-sectional study, addressing causality is difficult. The case-mix that has come to existence might reflect different prognosis. It is likely that the trend of better outcomes is associated with the change in patient population, however, this can not be distinguished from other changes that might have occurred during the observed years. The patients that initiated biologic treatment during the years 1999 and 2000 are likely to reflect a different population, because these patients have been waiting for etanercept to become available in daily clinical care.
Because of the observational nature of the study, some patients have discontinued the agents and switched to other treatment options. We therefore corrected the proportion of patients that achieved inactive disease for the fraction of patients still on the drug (LUNDEX method). The percentages of patients with LUNDEX-corrected inactive disease differed only slightly from the unadjusted percentages. For the longer-term follow-up these differences are expected to increase.

In conclusion, biologics are being prescribed increasingly and earlier in the disease course. While etanercept remains biologic of first choice for non-systemic JIA, anakinra has become first choice for systemic JIA patients. The JIA population taken into consideration for first biologic treatment has changed towards a less severely affected population and this change is accompanied by better short-term disease outcomes.

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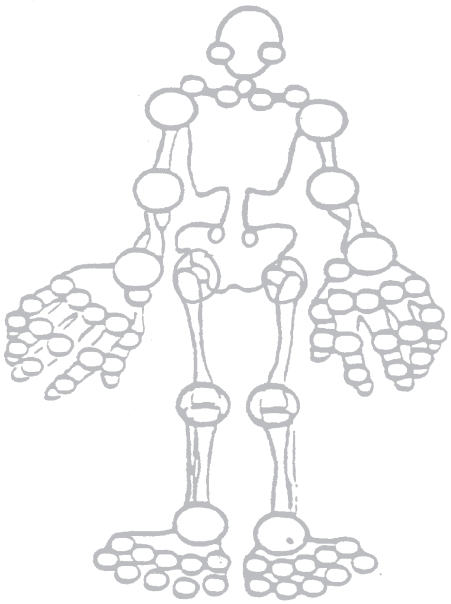
CHAPTER 5.2

Treatment choices of paediatric rheumatologists for JIA; etanercept or adalimumab?



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ABSTRACT

Objective: To evaluate differences between etanercept and adalimumab treated juvenile idiopathic arthritis (JIA) patients and to elucidate factors that influence these treatment choices of physicians.

Methods: JIA patients with active arthritis who initiated adalimumab or etanercept as first biologic agent between March 2008 and December 2010 were selected from the Dutch Arthritis and Biologics in Children register. Baseline characteristics of these patients were compared. Additionally, focus-group interviews with paediatric rheumatologists and rheumatologists were performed to evaluate factors that determined the treatment choices.

Results: A total of 181 JIA patients initiated etanercept and 13 adalimumab. The adalimumab-treated patients had longer disease duration prior to start biologic (median of 6.1 vs. 1.9 years) and more often a history of uveitis (85% vs. 3%). The etanercept-treated patients had prior to introduction more disability (median CHAQ score 1.1 vs. 0.3), more joints with active arthritis (median number of joints with arthritis 6 vs. 3) and more impact of the disease on parent/patient assessment of wellbeing (median score of 50 vs. 16 of 100).
The focus group interviews confirmed the preference for etanercept. The presence of uveitis was one of the most important factors that directed the choice towards adalimumab. But also a history of uveitis and an increased risk for the development of uveitis or inflammatory bowel diseases were mentioned factors to prefer adalimumab. The painful adalimumab injections and the more extensive experience with and existing scientific evidence for etanercept were the most important reasons to prescribe etanercept.

Conclusions: Etanercept is more often prescribed, but adalimumab is mainly preferred in the presence of uveitis. Patient-related factors specific for the paediatric population, like painful adalimumab injections, accounted for the preference of etanercept. Paediatric rheumatologists make rational decisions taken into account drug and patient factors and respond quickly to newly published data.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) patients refractory to high dose methotrexate (MTX) treatment are eligible for treatment with biologic agents. In 1999, etanercept, an anti-TNF alpha receptor-fusion protein, was the first biologic agent to be approved by the FDA for the treatment of poly-articular course JIA. Its efficacy and safety has been demonstrated in a randomized controlled trial (RCT) and several long-term observational studies, including the Dutch Arthritis and Biologics in Children (ABC) register.[1-3] In 2008 the second biologic agent adalimumab, a monoclonal anti-TNF antibody, was approved for poly-articular course JIA after its efficacy was established in a placebo controlled withdrawal trial.[4] Observational data on the use of adalimumab in the treatment of arthritis are limited.[5-6] But, adalimumab is considered to be the preferred biologic in treating uveitis.

The American College of Rheumatology has formulated recommendations concerning the initiation of TNF-alpha-inhibitors, but does not distinguish between the different anti-TNF agents.[7] In RA, adalimumab is considered as effective as etanercept in lowering arthritis disease activity[8], but for neither JIA nor adult RA head-to-head trials that compare etanercept and adalimumab directly exist. When deciding between these two biologic therapies, physicians can only rely on limited evidence and will also consider other factors.

Qualitative research can present additional information on these factors and can provide insight in how and why physicians make decisions when prescribing medication, which can not be deducted from quantitative studies, such as the ABC register.[9]

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

PATIENTS AND METHODS

Patient population and baseline data from the ABC register

This study is part of the ABC register, a national ongoing multicentre prospective study, which aims to include all Dutch patients with JIA treated with biologics. The ABC register contains prospectively obtained data since the introduction of biologic agents for JIA in 1999.

At baseline, data on demographics and disease characteristics were collected. The following baseline JIA disease activity scores (variables of the JIA core set) were retrieved:

physician's global assessment 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 a global assessment of pain by VAS is reported.
From March 2008, adalimumab became available for the treatment of JIA in daily care in the Netherlands. Therefore, for this analysis, biologically-naïve patients who initiated etanercept or adalimumab between March 2008 and December 2010 were selected from the ABC register. JIA patients without active arthritis, but who initiated biologics to treat solely the uveitis, are not consequently recorded in the ABC register and patients without active arthritis at baseline were therefore not included in the analyses.

Focus group methods

The qualitative part consisted of two focus group interviews. The interviews were carried out in October and November 2011. A total of 20 paediatric rheumatologists and rheumatologists involved in the care of paediatric patients, who were all members of the Dutch Society for Paediatric Rheumatology, were recruited by email. Forty percent of these physicians responded. The first focus group comprised two rheumatologists also treating paediatric patients and three paediatric rheumatologists. The second focus group comprised three paediatric rheumatologists. The participants worked in six different areas of the Netherlands and in seven different hospitals.
The first interview lasted one hour, the second interview 37 minutes. Two researchers were present: the moderator (rheumatologist also treating paediatric patients, SG) and the secretarial assistant (research physician in paediatric rheumatology, JA). The interview guide comprised questions on the perceived effectiveness of the two treatment options, the motivation for initiation of a certain biologic treatment, the experience of the physician with the different therapies and possible contra-indications. In addition the participants were confronted with the data retrieved from the ABC register and asked for their interpretation.
JA audio recorded and transcribed the focus group interviews verbatim. Transcripts were checked for accuracy and sent to all participants for checking. For analysis of the transcript a phenomenological approach was used.[10] The transcripts were read and reread to get a global impression, and the transcripts were subsequently coded following an open coding strategy by JA. In addition notes were made on comments that expressed emotions, beliefs, or explicit indicators of doubt, insistence or certainty. SG checked the coding and JA and SG discussed coding until consensus was reached. Subsequently key units were identified from the codes, and these were summarized in broader themes making note of their importance.

Statistical analysis

Descriptive statistics were presented as absolute frequencies or median values with IQR, unless otherwise specified. Differences between the two treatment groups with regard to patient and disease characteristics at baseline were compared using Fisher's exact test or Mann Whitney U whenever applicable. Differences were considered significant at a two-sided p-value <0.05. Data were analyzed using the SPSS for Windows package, version 17.0.2 (SPSS Inc., Chicago, Illinois, USA). MAXQDA 10 software was used to perform the analysis of the qualitative data.

RESULTS

Patients' characteristics from the ABC register

Between March 2008 and December 2010 a total of 181 previously biologically-naïve JIA patients had initiated etanercept and 13 adalimumab. The number of patients who started these biologics increased during the observed years. Patient and disease characteristics are presented in Table 1. Patients primarily treated with adalimumab had longer disease duration prior to introduction compared with patients treated with etanercept. Most patients (85%) treated with adalimumab had a history of uveitis. Two patients did not have a history of uveitis and these patients presented with the extended oligoarticular and the enthesitis-related arthritis subtypes. The disease activity at initiation of biologic therapy was higher for the etanercept-treated patients indicated by higher CHAQ scores, more joints with active arthritis and more impact of the disease on parent's or patient's assessment of wellbeing.

Qualitative focus group results

Etanercept and adalimumab were assumed to be equally effective. However, paediatric rheumatologists noted that they had less experience with adalimumab than their colleagues also treating adult RA patients. The main factors that influenced decision making are presented in box 1 and the highlighted citations are given in box 2. The factors that influenced decision making could be grouped in three broad categories; internal factors (related to the drug, the patients characteristics, or the doctor) external factors (related to brand awareness, service provided by pharmaceutical companies, governmental regulations and drug availability) and costs.

The themes most frequently discussed by both groups were pain and fear for injection, presence of uveitis and the existent experience with a drug. Issues concerning the administration of the treatment and the presence of symptoms possibly indicating inflammatory bowel disease (IBD) or enthesitis related arthritis (ERA) also received a lot of attention.

TABLE 1. Patient and disease characteristics

Characteristics	Etanercept (181)	Adalimumab (13)
Female (%)	117 (65)	8 (62)
Age at onset JIA, median (IQR), years	8.3 (2.9-11.7)	7.2 (1.9-9.8)
Age at start first biological, median (IQR), years	12.1 (7.2-14.7)	12.3 (10.0-15.3)
JIA disease duration before start biological, median (IQR), years	1.9 (1.1-4.3)	6.1 (2.7-8.8)*
Onset JIA subtype		
Systemic JIA (%)	11 (6)	-
Polyarticular RF neg (%)	75 (41)	3 (23)
Polyarticular RF pos (%)	20 (11)	-
Oligo extended (%)	37 (20)	5 (39)
Oligo persistent (%)	13 (7)	2 (15)
Arthritis psoriatica (%)	11 (6)	2 (15)
ERA (%)	14 (8)	1 (8)
History of uveitis (%)	6 (3)	11 (85)*
ANA pos (%)	76 (42)	8 (62)
HLA B27 pos (%)	14 (8)	1 (8)
RF pos (%)	18 (10)	-
Previously used medications		
Systemic prednisone (%)	69 (38)	6 (46)
Intra-articular prednisone (%)	60 (33)	7 (54)
Methotrexate (%)	181 (100)	13 (100)
Other synthetic DMARDs (besides methotrexate) (%)	9 (5)	1 (8)
Concomitant co-medication at baseline		
Systemic prednisone (%)	33 (18)	1 (8)
Intra-articular prednisone (%)	12 (7)	3 (23)
Methotrexate (%)	147 (81)	10 (77)
Other synthetic DMARDs (besides methotrexate) (%)	5 (3)	2 (15)
Disease activity scores at baseline:		
VAS physician, median (IQR)	50 (35-65)	38 (4-58)
CHAQ total, median (IQR)	1.13 (0.60-1.75)	0.25 (0.0-0.75)*
VAS pain, median (IQR)	52 (25-75)	33 (3-50)
VAS wellbeing, median (IQR)	50 (25-70)	16 (2-50)*
Active joints, median (IQR)	6 (4-10)	3 (2-5)*
Limited joints, median (IQR)	3 (1-6)	2 (1-3)
ESR (IQR), median (IQR), mm/hour	12 (6-28)	6 (2-21)

* significance level $p<0.05$

[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]

BOX 1. Factors mentioned influencing choice between etanercept and adalimumab

Internal factors

Drug related
- Side effects/safety
  - In general
  - Short term
    - Pain/fear
    - Infections
    - Other
  - Long term
    - Immunogenicity
    - Growth
    - Administration issues
    - Mechanism of action

Patient related
- Patient/parents choice
- Disease characteristics
  - Uveitis
  - ANA positive oligoarthritis (without uveitis)
  - ERA/ PsJIA/ IBD symptoms
  - Other subtypes of JIA
    - Age
    - Joint involved
    - Disease severity

Doctor related
- Existent experience/ clear preference for etanercept
- Gaining experience with a new drug/specifically not
- Feeling/morality
- Practice of evidence based medicine

External factors

Brand awareness
Service pharmaceutical company
Governmental regulations
Drug availability

Costs (when other than standard dosing)

Pain on injection was the most important drug-related factor mentioned. All physicians agreed that paediatric patients experienced the injections of adalimumab as very painful.(Citation 1) They also noted that the prefilled formulation of etanercept is perceived to be irritating. The self-dissoluble formula of etanercept was therefore preferred by most. Availability of a formulation specifically adapted for paediatric use was seen as an advantage of etanercept, and although adalimumab has recently improved its paediatric formulation, it was still thought to be less practical.

BOX 2. Highlighted citations

Citation	
1	*"… why is adalimumab prescribed so infrequently to children? Well I can give you a very simple answer; because it's painful!!"*
2	*"… In recent years it has been shown that etanercept might be less effective for uveitis…resulting in the fact that, when I am considering anti-TNF prescription for a child which has or has had severe uveitis, I would choose adalimumab in the first place."*
3	*"We also have a group of patients -- I know, this is absolutely not evidence based – 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."*
4	*".. that brings me back to the fact of our experience in adults, we obviously have this long-lasting experience with adalimumab, for me at least [lack of experience with adalimumab] is not a reason not to start treatment with adalimumab in a child."*
5	*Citation 5: "…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."*

Adalimumab was preferred by all physicians when uveitis was present.(Citation 2) Two physicians would consider prescribing it for patients with ANA-positive oligo-arthritis. These patients have a higher risk of developing uveitis.

Physicians also considered treatment with adalimumab in patients who keep having complaints suspect for IBD, but in whom IBD could not be confirmed.(Citation 3) Other indications mentioned for prescribing adalimumab rather than etanercept were enthesitis related arthritis and psoriatic arthritis.

A doctor-related factor hat received a lot of attention, was experience. Gaining experience with a new treatment was a consideration to prescribe adalimumab. Most physicians however strongly indicated etanercept to be their first choice, relying heavily on the available evidence and their personal familiarity with the drug. This was different for the rheumatologists also treating adult RA patients. Their experience with adalimumab was more extensive and they were therefore less reluctant to prescribe this treatment to children.(Citation 4)

Finally, practicing evidence based medicine featured prominently in the discussions. It was clear that all physicians were aware of the novelty of these treatments. Therefore, during the interviews, they were constantly referring to literature and evidently trying to base their decisions on the latest research.

No pressure from the industry was noted, apart from a few comments on advertisements received from and questions asked by the visiting delegates of the pharmaceutical companies. However, two physicians did suggest that marketing and brand awareness played a role in the consideration to prescribe certain treatments.(Citation 5) Costs were only touched upon marginally, especially when dosages other than the standard dosage were considered. When prescribed in standard dosage, etanercept and adalimumab are

equally expensive (costs for standard use of 15 days in the Netherlands: etanercept EURO 597.75 / USD 787.86, adalimumab EURO 607.11 / USD 797.53).[11] External factors and costs were mentioned, but not as a primary reason to choose one of the TNF inhibitors.

DISCUSSION

This study shows that both etanercept and adalimumab are being prescribed increasingly. The absolute numbers indicated that etanercept is still preferred by the paediatric rheumatologist, which the focus group interviews confirmed. Patients to whom adalimumab was prescribed were characterised by a history of uveitis, longer disease duration and lower disease activity. The presence of uveitis was acknowledged by the interviewed physicians to be one of the most important factors that directed their choice towards adalimumab. The painful adalimumab injections and the more extensive experience with and existing scientific evidence for etanercept were the most important reasons to be reticent with the prescription of adalimumab.

From this study it appears that refractory JIA-associated uveitis constitutes a reason to consider treatment with a biologic agent, which is supported by the literature. In contrast to the proven efficacy of etanercept on the arthritis, results of etanercept in the treatment of refractory uveitis are less satisfactory.[12-13] Based on mainly retrospective case series, adalimumab and infliximab seem to be more effective than etanercept and adalimumab is now considered to be the preferred biologic treatment of childhood uveitis.[14-18]

The fact that uveitis might contribute to the decision to initiate adalimumab may account for the longer disease duration before initiation of adalimumab. Uveitis develops most often in the oligo-articular subtypes, which formed the largest part of the adalimumab-treated group and are generally controlled for a long time by treatment-modalities other than TNF blockers. In addition, the arthritis frequently precedes the uveitis and is not always active enough by itself to be considered for biologic treatment.[19] Uveitis as a factor contributing to the decision to prescribe adalimumab may also explain why disease activity scores (related to arthritis) were lower in patients treated with adalimumab. The subtypes ERA, psoriatic arthritis and oligo persistent arthritis comprised more than one-third of the patients treated with adalimumab, in line with the indications to consider adalimumab mentioned during the focus group interviews. Spondylarthritides are associated with psoriasis and IBD and TNF-alpha also plays a role in the pathogenesis of psoriasis and IBD. TNF inhibitors seem to be equally effective for joint symptoms, but on gut manifestations monoclonal antibodies against TNF-alpha such as adalimumab seem to be more effective than etanercept.[20-21]

The present study indicates that the process of prescribing new drugs is complex and time consuming and involves many factors in addition to the effectiveness of the drug for the indication in question. This is in line with other studies performing qualitative research eliciting on factors associated with prescription patterns.[22-26] Deducted from the focus group interviews performed, these factors were put together in three categories; internal factors, external factors and costs. The same structure of influencing factors has been described before in a qualitative study on prescription patterns of general practitioners when confronted with the choice between multiple drugs in one therapeutic group.[23] In the general practitioners office costs played a much more important role than it did in the current study. The medication prescribed in the specialised field of paediatric rheumatology is generally more expensive than the medication prescribed by general practitioners. Additionally the costs of TNF-inhibitors are approximately the same, but differences might exist when these agents are prescribed in other than standard dosages. Costs are apparently a secondary factor that comes into play when more experience is built up with the new drug. It could also be that moral resistance is felt against cost-conscious statements. Although a notion of cost-effectiveness should be present, doctors feel that the emphasis should be on patient-centred factors rather than financial considerations.[24-25]

This study is limited in its size. Because only few patients received adalimumab, these data should be interpreted with caution. The ABC register focuses on paediatric patients with arthritis and patients initiating biologic therapy solely for JIA-associated uveitis could therefore not be discussed.
Not all rheumatologists and paediatric rheumatologists invited for focus group interviews responded. It might therefore be that the influential factors identified are not representative for all Dutch physicians treating JIA patients with biologics. Nevertheless, in both interviews the same considerations were mentioned and we feel no topics were left out. The researcher that moderated the interview was experienced in qualitative research. However, she was also a rheumatologist herself, which brings along the risk of peer reviewing, by which she might have influenced the interviewees with her own opinion on the subject.

In conclusion, etanercept is more often prescribed by paediatric rheumatologists than adalimumab. Patient characteristics differed between the two treatment-groups, the most important one being the presence of and risk for uveitis in the adalimumab treated patients. In deciding which biologic to prescribe to the biologically-naïve patient, paediatric rheumatologists make rational decisions. They take into account drug and patient factors and respond quickly to newly published data. Experience built up with

the longer available drug, in this case etanercept, contributes largely to the persisting preference for etanercept. Drug marketing and costs play a minimal role in this process.

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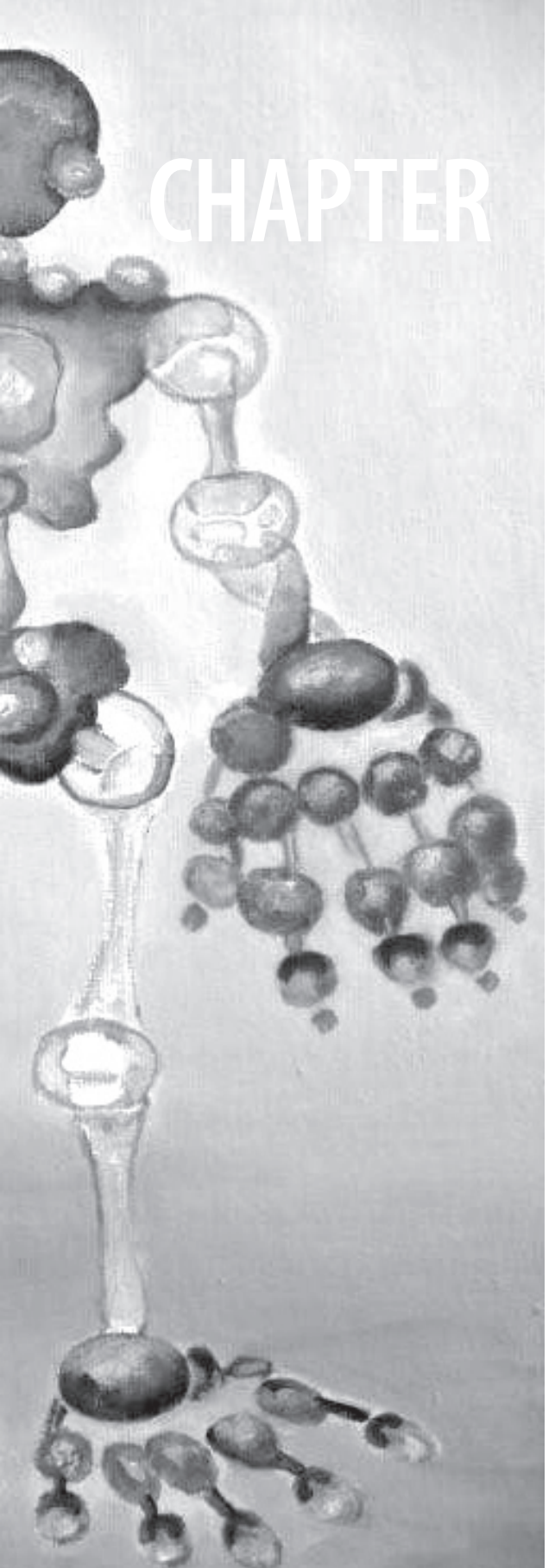
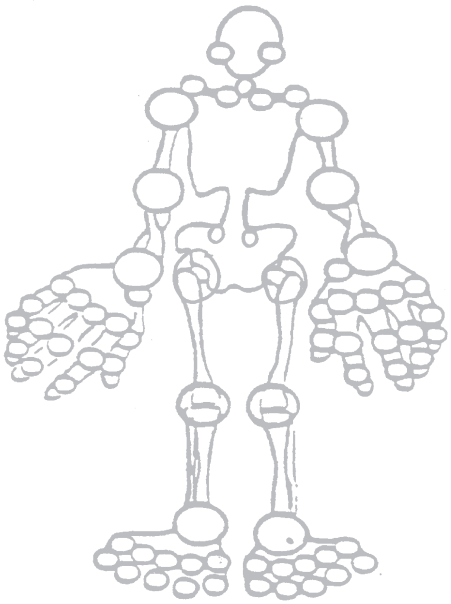


CHAPTER 6

Addendum

CHAPTER 6.1

The Toll-like receptor 4 agonist MRP8 and MRP14 protein complex is a sensitive indicator for disease activity and predicts relapses in Systemic-Onset JIA



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ABSTRACT

Background: Analysis of myeloid-related protein 8 and 14 complex (MRP8/14) serum concentrations is a potential new tool to support the diagnosis of systemic-onset juvenile idiopathic arthritis (SJIA) in the presence of fever of unknown origin.

Objective: To test the ability of MRP8/14 serum concentrations to monitor disease activity in patients with SJIA and stratify patients at risk of relapse.

Methods: Serum concentrations of MRP8/14 in 52 patients with SJIA were determined by a sandwich ELISA. The monitoring of therapeutic regimens targeting interleukin 1 and tumour necrosis factor α, and methotrexate treatment was analysed and diagnostic power to predict flares was tested.

Results: MRP8/14 levels were clearly raised in active disease and decreased significantly in response to successful treatments. Serum concentrations of MRP8/14 increased significantly ($p<0.001$) (mean±95% CI 12.030±3.090 ng/ml) during disease flares compared with patients with inactive disease (864±86 ng/ml). During clinical remission MRP8/14 serum levels of >740 ng/ml predicted disease flares accurately (sensitivity 92%, specificity 88%). MRP8/14 levels correlated well with clinical disease activity, as assessed by physician's global assessment of disease activity ($r=0.62$), Childhood Health Assessment Questionnaire ($r=0.56$), active joint count ($r=0.46$) and with C-reactive protein ($r=0.71$) and erythrocyte sedimentation rate ($r=0.72$) (for all $p<0.001$).

Conclusion: MRP8/14 serum concentrations correlate closely with response to drug treatment and disease activity and therefore might be an additional measurement for monitoring anti-inflammatory treatment of individual patients with SJIA. MRP8/14 serum concentrations are the first predictive biomarker indicating subclinical disease activity and stratifying patients at risk of relapse during times of clinically inactive disease.

INTRODUCTION

Systemic-onset juvenile idiopathic arthritis (SJIA) is an aggressive auto-inflammatory disease presenting with arthritis, high spiking fever, erythematous rash, lymphadenopathy, hepatosplenomegaly and serositis.[1] However, characteristic autoimmune features are not present in SJIA and typical clinical signs such as arthritis may be absent at the onset of disease and especially in patients experiencing a disease flare while receiving anti-inflammatory treatment.

It has already been shown that myeloid-related proteins (MRP) 8 (S100A8) and 14 (S100A9) are useful serum markers for the diagnosis of SJIA in the presence of fever of unknown origin.[2] The myeloid- related protein 8 and 14 (MRP8/14) complexes are secreted after activation of phagocytes via a so called alternative secretory pathway[3–5] and cause strong proinflammatory effects on phagocytes and endothelial cells in vitro.[6 7] They act by binding to Toll-like receptor 4 (TLR4) and form a positive feedback loop with interleukin 1β (IL-1β) in SJIA.[2] The loss of control over secretory processes involving the IL-1 family and the damage-associated molecular pattern (DAMP) molecules MRP8/14 may contribute to the pathogenesis of SJIA.[2] MRP8 and MRP14 are calcium-binding proteins expressed in granulocytes, monocytes and macrophages during early differentiation stages. Since the activation of the innate immune system is a hallmark of the pathogenesis of SJIA,[3 8] MRP8/14 serum concentrations seem to be a good candidate marker for monitoring disease activity as has been already shown in other auto-inflammatory diseases.[9] Furthermore, MRP8/14 serum concentrations can detect subclinical inflammation in non-systemic JIA and indicate a higher risk of relapse after discontinuation of anti-inflammatory treatment.[10]

The aim of this work was to evaluate MRP8/14 serum concentrations in relation to disease activity and to investigate if it is a useful tool to affirm reactivation of SJIA and response to anti IL-1 and anti-tumour necrosis factor (TNF) agents. Furthermore, we studied if MRP8/14 serum concentrations can detect subclinical inflammatory activity that predisposes to reactivation of the disease.

PATIENTS AND METHODS

Patients with systemic-onset JIA

In total, serum samples from 52 patients (median age (range) 11 (2–21) years) who fulfilled the International League of Associations for Rheumatology criteria for SJIA[11] were prospectively obtained during the course of disease. Serum samples and routine laboratory parameters were obtained and clinical disease status was recorded at the time of patient examinations. MRP8/14 serum levels were analysed retrospectively and did not

influence clinical decisions in the participating centres. The study was approved by the institutional ethics committees, and informed consent was obtained from patients or parents.

Correlation between disease activity and MRP8/14 levels

In 45 of 52 patients (male/female: 20/25, age at disease onset, median (range): 5.7 (2–15) years; follow-up period, median (range): 52 (12–120) months) serum was collected regularly every 3–6 months at control visits or when disease activity changed, analysed at the end of the study and correlated with disease activity (samples/patient, mean (range) 11.5 (6–55)). In the remaining seven patients, only data before and after methotrexate (MTX) treatment were available.

Follow-up and subgroup analysis of patients with inactive disease

From the 45 patients mentioned above, 26 patients in remission on medication or with inactive disease off medication were followed up over 6 months with continuous examinations and sample collection at intervals of about 3 months. Patients were included only if they fulfilled the remission criteria and had a complete set of serum samples. Patients without apparent disease activity for at least 6 subsequent months were characterised as 'non-relapsers'. Patients who experienced a relapse within 6 months were characterised as 'relapsers'. MRP8/14, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), high-sensitivity CRP (hsCRP) and ferritin levels were compared during times of remission in both groups in order to investigate the predictive value of these inflammation markers to indicate imminent disease flares.

MRP8/14 concentrations during response to treatment

In 24 of 52 patients response to treatment was analysed. Twelve patients were treated with MTX (13.0–20.6 mg/m2) either orally (five patients) or subcutaneously (seven patients) once a week and were followed up for 6 months. Six patients were treated with recombinant IL-1 receptor antagonist (IL-1Ra) anakinra (Kineret, Amgen, Cambridge, UK; 2 mg/kg/day administered subcutaneously) and were followed up for 9 months. MRP8/14 levels were further analysed before discontinuation of IL-1Ra in four of these patients after a minimum of 12 months of treatment. In six patients, treatment with the soluble TNF-alpha receptor fusion protein etanercept (Enbrel, Wyeth, Muenster, Germany; 0.8 mg/kg/week or 0.4 mg/kg/twice weekly administered subcutaneously) was monitored for 12 months.

Clinical assessment of disease activity

Clinical disease activity was determined according to the core set criteria for JIA.[12 13] Patient data collected included medical history, physical examination, number of joints

with active disease, number of joints with limited motion, physician's global assessment of disease activity and parent's/patient's assessment of overall well-being (as measured by the Childhood Health Assessment Questionnaire (CHAQ)). The Juvenile Arthritis Disease Activity Score (JADAS) score was calculated retrospectively.[14] Leucocyte count, ESR and CRP levels were determined as measures of inflammation (table 1). CRP levels <5 mg/l were defined as normal values, according to the manufacturer. Serum samples of patients taken during acute infections were excluded from the analysis. Patients were categorised as having active disease (presence of any joint with active disease or signs of systemic disease) or were considered to have inactive disease or disease in remission based on the proposed preliminary criteria[15], including the absence of any systemic symptoms, no active arthritis, and normal CRP and ESR, regardless of medication.[16] Relapse was defined according to the preliminary definition of disease flare in JIA.[16]

TABLE 1. Characteristics of the patients with active SJIA (new onset or flare) or inactive disease

Characteristics	Inactive disease	Active SJIA	
		Flare	New onset
Samples, n	270	162	20
Patients, n	45	34	20
MRP8/14 level, ng/ml	846±86	12,030±3,090	24,750±11,410
ESR, mm/h (<20 mm/h)	8±1	35±4	54±14
CRP level, mg/l (<5mg/l)	<5mg/l	51±84	101±50
Joints with active disease, median (range)	0	5 (2-7)	8 (3-12)
Leucocytes, µl	7,130±275	12,680±1100	16,210±3,260

*Except where indicated otherwise, values are the mean±95% CI.
[CRP, C- reactive protein; ESR, erythrocyte sedimentation rate; MRP8/14, myeloid-related protein 8 and 14 complex; SJIA, systemic-onset juvenile idiopathic arthritis]

Determination of normal MRP8/14 serum levels

Normal MRP8/14 serum concentrations were determined in 50 healthy control individuals without signs of inflammation who were routinely examined at the University Children's Hospital Muenster or who were volunteering laboratory workers. Controls were age-matched to the study group. As previously described, there were no significant differences in serum MRP8/14 concentrations according to age or sex distribution.[3] The upper limit of MRP8/14 concentrations in healthy controls was defined as mean plus two SDs.

Laboratory measures

Serum concentrations of MRP8/14 were determined by sandwich ELISA as described previously.[3] For comparison with earlier studies, internal control serum samples were

used as a reference in all ELISA studies. The readers of the laboratory assay were blinded for diagnosis and inflammatory activity of the patients. A hsCRP test measuring low levels of CRP using laser nephelometry and ferritin analysis by a luminescence immunoassay were applied.

Statistical analysis

Analysis of variance was used to study differences between patient subgroups. Confirmed differences were tested for statistical significance using subsequent selective post hoc testing as described by Dunnett and Tamhane. Rank differences were analysed using the Mann–Whitney U test. Correlations were calculated using Spearman's ρ. Receiver operating characteristic (ROC) curves were plotted to determine the accuracy of inflammation marker measurements as a diagnostic test for a flare. Cox proportional hazards multiple regression analysis was performed to assess the predictive power of laboratory parameters for the risk of relapse. For this analysis, the probability of relapse developing within 6 months (in the presence of abnormal laboratory parameters) in patients with clinically inactive disease was tested. For relapsers, the last blood sample obtained before a relapse was included. For non-relapsers, samples obtained up to 6 months before the end of the individual follow-up periods were included. PASW Statistics 18.0 for Windows (SPSS, Chicago, Illinois, USA) was used for statistical analyses. Unless stated otherwise, data are expressed as the mean±95% CI.

RESULTS

MRP8/14 concentrations reflect disease activity in systemic JIA

Forty-five patients with SJIA were followed up through the course of disease. Samples were obtained at disease onset (20 patients), during disease flares (34 patients) and during inactive disease (all 45 patients).(Table 1) Serum levels of MRP8/14 in patients with new-onset SJIA were significantly raised (mean±95% CI 24.750±11.410 ng/ml) compared with patients with flares (12.030±3.090 ng/ml; $p<0.01$) and with healthy controls (310±40 ng/ml; $p<0.001$). MRP8/14 levels among patients with SJIA with inactive disease (864±86 ng/ml) were significantly lower than in patients with active disease but not significantly different from those of healthy controls (Figure 1A). Patients with clinical remission on medication (CRM) and inactive disease (ID) on and off medication did not reveal significant differences in MRP8/14 serum levels. ROC analysis demonstrated a better diagnostic accuracy for MRP8/14 than for ESR and CRP to detect flares. The area under the curve was 0.957±0.019 for MRP8/14, 0.893±0.043 for CRP and 0.889±0.038 for ESR (figure 1B). An MRP8/14 cut-off concentration of 2100 ng/ml had a sensitivity of 92% and specificity of 83% for the diagnosis of a relapse (positive likelihood ratio 11,

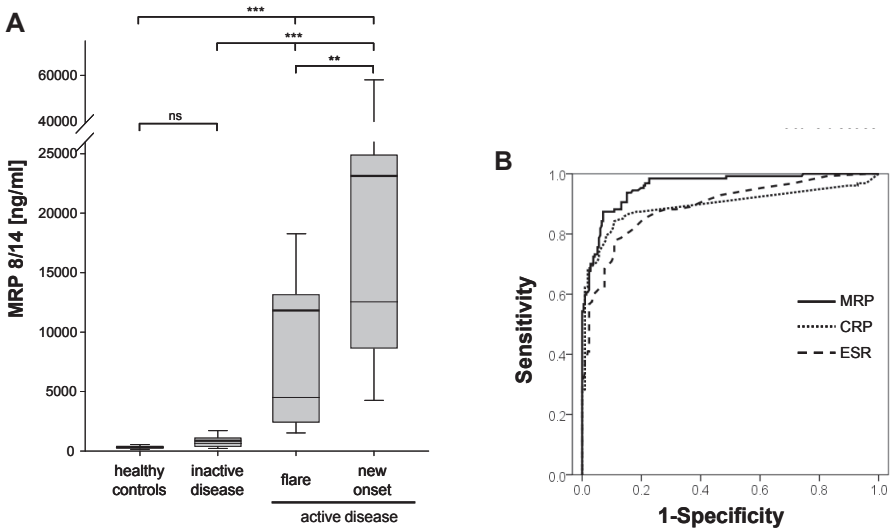

FIGURE 1. MRP 8/14 concentrations and disease activity in SIA
(A) Serum concentrations of myeloid-related protein 8 and 14 protein complex (MRP8/14) in patients with active (new-onset and flare) and inactive systemic-onset juvenile idiopathic arthritis (JIA). Also shown is the serum concentration of MRP8/14 in a group of healthy controls. Box plots show the median (thin horizontal line), the mean (thick horizontal line), and the 25th and 75th centiles. Bars indicate the 10th and 90th centiles. There was a significant difference in MRP8/14 concentrations between patients with active and inactive systemic-onset JIA (***p<0.001) or healthy controls (***p<0.001) (note the break in the y-axis). (B) Receiver operating characteristic curve analysis of MRP8/14, C-reactive protein concentrations (CRP) and erythrocyte sedimentation rate (ESR) displayed as sensitivity against 1–specificity for the differentiation between flare and inactive systemic-onset JIA.

negative likelihood ratio 0.18). There was a strong correlation between MRP8/14 and the active joint count (r=0.46), physician's global assessment of disease activity (r=0.62), CHAQ (r=0.56) and JADAS (r=0.62); MRP8/14 also correlated with concentrations of CRP (r=0.71), ESR (r=0.72) and absolute leucocyte count (r=0.59) (for all p<0.001).

Predictive value for the risk of relapse

Since a significant number of patients with inactive SJIA whose disease was considered to be in remission still had abnormal MRP8/14 levels, we were interested in the further outcome of these patients. In total, 13 of 26 patients who had been continuously followed up at 3-month intervals after induction of remission on medication or with ID off medication (Table 2) had a relapse within the follow-up period (Figure 2A,B). The MRP8/14 levels of these relapsers were increased in samples obtained up to 6 months before relapses (1000±206 ng/ml) compared with levels of non-relapsers (458±151 ng/ml) (p<0.001). Significant differences between patient groups with CRM or ID off and on medication could not be found. ROC analyses demonstrated a high diagnostic accuracy

TABLE 2. Characteristics of systemic-onset juvenile idiopathic arthritis patients with a relapse ('relapsers') or stable remission ('non-relapsers') within 6 months follow-up.

Characteristics	Relapser	Non-relapser
Patients, n	13	13
Sex (male/female)	6/7	7/6
Age, years, median (range)	7 (3.4-19.1)	11 (3.3-16.4)
Age at disease onset, years, median (range)	5 (1.9-13.3)	4 (2.3-14.5)
Duration of disease years, median (range)	6 (1.2-13.9)	5 (1.1-12.9)
Clinical remission while receiving medication, months, mean (range)	4.1 (1-7)	6.5 (1-24)
Inactive disease while not receiving medication, months, mean (range)	3.3 (1-6)	8
Course of treatment	*Stable/taper/disc*	*Stable/taper/disc*
PRE	1/0/0	0/1/0
AZA/PRE	-	0/1/0
MTX/PRE	2/3/0	1/0/1
MTX/anti-TNF	1/0/0	1/0/1
Anti-IL-1	2/0/1	6/0/0
No treatment	3	1

Course of treatment indicates whether the patients were on a stable treatment, tapered the dose or discontinued treatment after inclusion
[AZA, azathioprine; disc, discontinuation; IL, interleukin; MTX, methotrexate; PRE, lowdose prednisolone (≤0.2 mg/kg); TNF, tumor necrosis factor]

for identifying patients at a higher risk of relapse (area under the curve 0.91; p<0.001) (figure 2C). At a cut-off level of >740 ng/ml the test had a sensitivity of 92% and a specificity of 88% to identify patients at risk of relapse, the negative likelihood ratio within the following 3-6 months with MRP8/14 serum concentrations <740 ng/ml was 0.125, which is considered excellent for a diagnostic test.[19] By definition, during remission the patients had negative CRP (<5 mg/l) and normal ESR (<20 mm/h) at baseline. Figure 2D shows the cumulative proportional remission in patients with low versus high MRP8/14 levels; exclusion of patients with ID off medication did not change the statistics significantly.
These data suggest that MRP8/14 levels are predictive of a relapse up to 6 months before the clinical relapse occurs. Since CRP and ESR have to be normal in remission, we compared the predictive value of the more sensitive inflammation markers hsCRP and ferritin with the predictive value of MRP8/14. None of these additional markers predicted the outcome of patients in remission (Table 3).

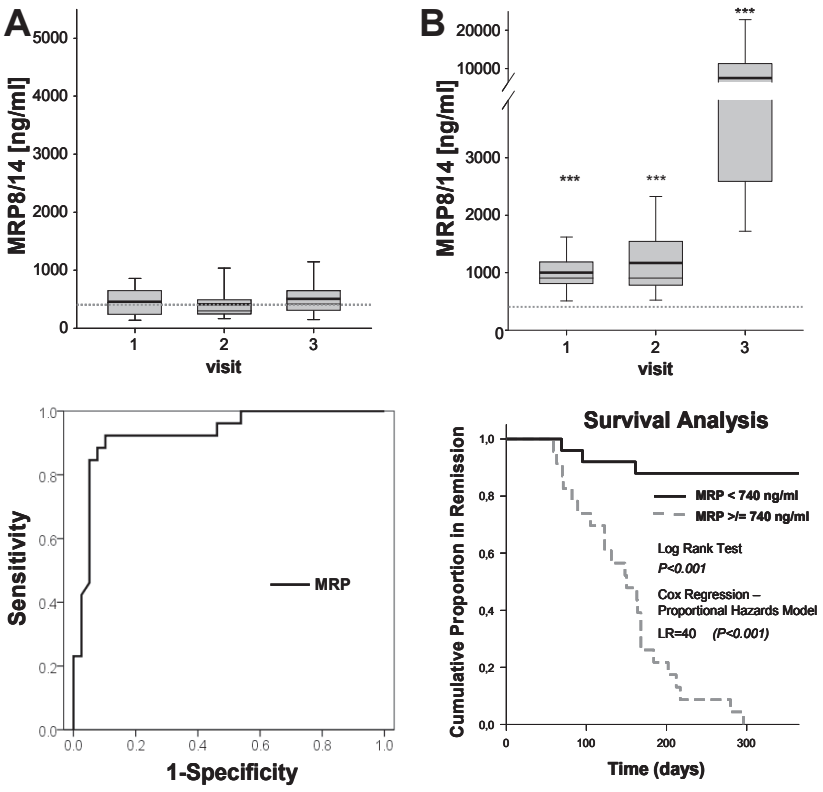

FIGURE 2. Individual follow-up of patients with systemic-onset juvenile idiopathic arthritis
(A) In 13 patients who were followed up during routine examinations at 3-month intervals, disease remained in stable remission for 6 months after inclusion. The myeloid-related protein 8 and 14 complex (MRP8/14) serum concentrations remained low in these patients over the whole follow-up period. (B) In samples obtained from 13 patients on remission, before a relapse occurred, MRP8/14 concentrations were higher than those in samples obtained from patients with stable remission (***p<0.001 vs A). The grey dotted line represents the normal range. (C) Receiver operating characteristic curve analysis of MRP8/14 concentrations displayed as sensitivity against 1–specificity for the differentiation between patients experiencing a flare and patients in stable remission. (D) Cox proportional hazards multiple regression analysis confirmed the significant association between MRP8/14 serum levels and risk of relapse. The black line represents cumulative remission of patients with MRP8/14 serum concentrations of up to 740 ng/ml, while the light grey broken line represents cumulative remission of patients with higher MRP8/14 levels. The latter group had significantly more relapses within a follow-up period of 6 months. LR, likelihood ratio.

TABLE 3. Inflammation markers in patients experiencing a relapse (visit 3) (n=13) or being in stable remission over the follow-up period of at least 6 months (n=13)

	One (6 months before flare/ remission)				Two (3 months before flare/ remission)				Three (flare/remission)			
Visit	**MRP8/14**	**hsCRP**	**Ferritin**	**ESR**	**MRP8/14**	**hsCRP**	**Ferritin**	**ESR**	**MRP8/14**	**hsCRP**	**Ferritin**	**ESR**
Flare	1000±206	0.06±0.04	36.2±13.8	10±3.1	1168±362	0.12±0.08	45.5±22.5	10.3±3.0	7520±4463	3.9±1.9	640.6±444.5	34.2±12.4
Remission	458±151	0.08±0.07	32.3±11.8	6.5±2.8	361±183	0.06±0.03	33.6±11.2	7.9±2.2	523±203	0.22±0.2	61.9±42.2	5.2±3.1
P Value	<0.001	0.65	0.45	0.06	<0.001	0.69	0.52	0.07	<0.001	<0.001	<0.001	<0.001

Values are the mean±95% CI.

[ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C reactive protein; MRP8/14, myeloid-related protein 8 and 14 complex]

MRP8/14 concentrations before discontinuation of IL-1Ra treatment

Four patients (three boys aged 15, 18 and 21 years and one girl aged 14 years) with stable remission and receiving IL-1Ra treatment without concomitant steroid-treatment or other anti-inflammatory drugs were included. MRP8/14 levels were prospectively analysed every 3 months during continuing treatment with IL-1Ra. Treatment was discontinued before the last visit and two patients with raised MRP8/14 levels before discontinuation of treatment had a flare of disease while the other two patients with MRP8/14 levels within the range of healthy controls remained in remission without medication for at least a further 3 months, underlining the predictive value of MRP8/14 levels for the identification of stable remission.

MRP8/14 concentrations: treatment with MTX

Samples from 12 patients were analysed before and 6 months after MTX treatment was started. All patients were concomitantly treated with oral prednisolone (0.05–2 mg/kg); two of the responders and one non-responder were also treated with intravenous methylprednisolone (30 mg/kg). Initial MTX dosages were between 13 and 15 mg/m2/week and were escalated in certain patients. Six patients (14.6–17.4 mg/m2 MTX, applied orally in three patients and subcutaneously in three patients) responded to treatment (American College of Rheumatology (ACR) 70 or complete response) and showed a strong reduction of MRP8/14 levels after 6 months of treatment (figure 3A). Six patients (13.1–22.0 mg/m2 MTX applied orally in two patients and subcutaneously in four patients) who did not respond or had a weak response (ACR 30) showed constantly raised or only slightly decreasing MRP8/14 levels (figure 3B).

MRP8/14 concentrations: treatment with biologic agents (IL-1Ra and anti-TNF-alpha treatment)

Samples obtained from six patients who were treated with IL-1Ra owing to failure of other anti-inflammatory treatments were analysed before anakinra was started and after 1, 3 and 6–9 months. We found an impressive decrease in MRP8/14 concentrations after initiation of IL-1Ra treatment, which was stable for at least 6 months (figure 3C). Samples obtained from six patients were analysed before etanercept treatment was started and after 3 and 12 months (figure 3D). MRP8/14 concentrations decreased markedly after initiation of treatment and response was stable for at least 12 months. The response in both groups was paralleled by a significant decrease in disease activity (number of active joints, CRP, ESR).

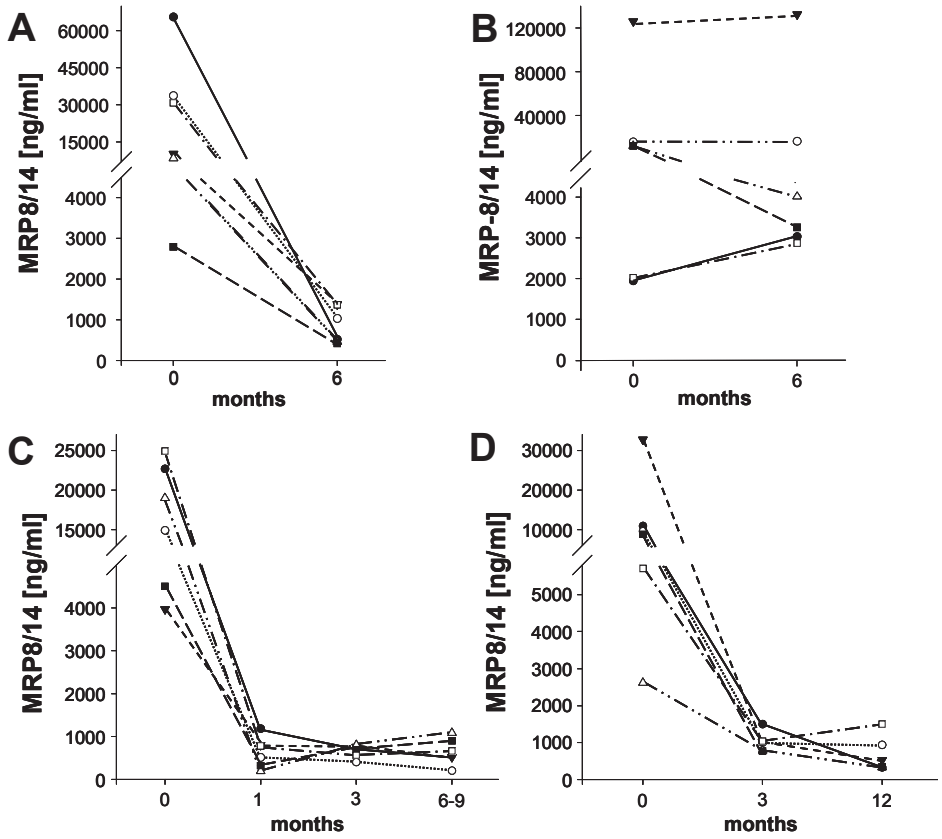

FIGURE 3. Decrease of myeloid related protein 8 and 14 complex (MRP8/14) in response to treatment (A, B) Twelve patients with systemic-onset juvenile idiopathic arthritis (SJIA) were treated with 13.0–20.6 mg/m2 methotrexate once weekly. Samples were obtained before the start of treatment and after receiving medication for 6 months. A significant decrease in MRP8/14 serum levels was seen in those patients responding to treatment (A), while patients without response or response grade ACR30 showed constantly raised MRP8/14 serum levels (B). (C) Remission was induced in six patients with SJIA treated with 2 mg/kg interleukin 1 receptor antagonist daily. Samples were obtained before the start of treatment and after receiving medication for 1, 3 and 6–9 months. (D) Remission was induced in six patients with SJIA treated with etanercept 8 mg/kg weekly or 4 mg/kg twice weekly. Samples were obtained before the start of treatment, and after 3 and 12 months from patients with clinically inactive disease. A significant decrease in MRP8/14 levels was seen in all patients responding to treatment.

DISCUSSION

The diagnosis of SJIA and its further management is still a major challenge for paediatric rheumatologists. In a recent study we showed that serum concentrations of MRP8/14 measured in samples from patients with SJIA are in a range not found in other inflammatory conditions.[2] This is of significance because MRP8/14 belongs to the DAMP family of molecules and acts as an endogenous activator of TLR4, which is involved in inflammatory processes of arthritis and autoimmunity.[17–19] Both proteins are released after inflammatory activation of phagocytes and their serum concentrations correlate well with phagocyte activity in different inflammatory diseases.[3, 9] It is well known that high concentrations of IL-1 are not found in SJIA.[20] However, the biologic relevance of IL-1 is confirmed by the efficiency of anti-IL-1 treatment in SJIA. We have shown that MRP8/14 is the serum factor responsible for IL-1β release in systemic-onset JIA.[2] While IL-1 measurements are of little help in the clinical routine setting, MRP8/14 are stable proteins that can easily be analysed, thus providing insight into the activation of immune mechanisms involving the IL-1 axis that is crucial during SJIA.[2]

When the diagnosis of SJIA has been established, therapeutic approaches aim to suppress inflammation, resulting in disease remission. However, the assessment of innate immune activity is not easy, although it is probably the key to successful disease management in SJIA. In addition, SJIA is a heterogeneous entity. It has been shown that a variable number of patients with SJIA do not respond to IL-1 blockade.[21–23] Therefore there has been discussion as to whether SJIA encompasses different subtypes or stages defined by their response to anti-IL-1 treatment. Regardless of the chosen drug—that is, methotrexate or biologic agent—our results suggest that MRP8/14 serum concentrations closely reflect disease activity, response to treatment and also, failure of response to treatment. The additional ability to detect disease flares with a higher sensitivity than CRP or ESR makes the assessment of these biomarkers a valuable tool in the clinical follow-up of patients with SJIA. Acute infections have to be ruled out in patients to avoid false-positive results.

While most patients benefit from the treatments temporarily, many of them have recurrent disease activity after tapering or withdrawing treatment. Only 53% of patients with JIA treated with etanercept retain remission over a median of 0.8 years after discontinuation of treatment.[24] Therefore a thorough immune surveillance and evaluation of disease activity is important in monitoring the success of treatments and in detecting subclinical immune activation that may predispose the patient to relapse. With the tools available to date, it is not possible to predict the outcome after stopping treatments. With our present results we show the sensitivity of MRP8/14 serum levels (95%) to differentiate

patients in remission on medication as prone to a relapse or not. Remission in patients with SJIA should not only be defined by clinical symptoms or raised CRP or ESR levels. We suggest that the status of 'immunological remission' should include additionally determination of MRP8/14 serum levels.[3,25] Our analysis of IL-1Ra-treated patients with SJIA in remission on medication confirmed these results. In a recent controlled trial the ability of these biomarkers to predict a relapse after withdrawal of MTX in non-systemic JIA has already been shown.[10] In SJIA, suboptimal disease control in patients with ongoing inflammatory activity may predispose the patient to both disease flares and to long-term systemic complications.

Although this is the largest biomarker study in SJIA, our study has some limitations owing to the number of cases. Since SJIA is a rather rare disease, it is not easy to collect patient cohorts systematically. Therefore, serum was collected from patients with SJIA regardless of the severity of the disease. No patients were excluded from the analysis, if clinical diagnosis of SJIA was once established. Study of larger cohorts will be important to further prove the accuracy of MRP8/14 analysis in this context. Interleukins as biomarkers in SJIA are discussed as well. Peripheral blood mononuclear cells from patients with SJIA were shown to release higher amounts of IL-1 in the study by Pascual *et al*, while Gattorno *et al* could not find raised IL-1 levels in patients with SJIA.[23] IL-6 seems to have an important role in the pathogenesis of SJIA and as a biomarker in active disease.[26] Its importance has been shown by the good response of patients with SJIA to the anti-IL-6 antibody tocilizumab.[27] However, another study showed that IL-6 and other pro-inflammatory cytokines such as IL-12 and TNF-alpha are upregulated in all active categories of JIA. In contrast, IL-18 can identify active patients with SJIA among other JIA categories; no prospective data during the course of SJIA are available.[20] Although tools for analysis of interleukin are available, their usefulness for monitoring disease activity has not been demonstrated. A major problem in daily practice is the degradation of these cytokines,[28] whereas MRP8/14 complexes are stable, which enables sending samples at room temperature and long-term storage.

Together, our study shows that analysis of MRP8/14 serum concentrations is a useful tool for monitoring disease activity in SJIA. It confirms the diagnosis of relapses and reflects response to treatment with different treatment regimens. Furthermore, MRP8/14 levels reflect continuing subclinical inflammatory activity in patients with clinical remission and can identify patients at risk of relapse. Therefore they are a potentially new tool for therapeutic management and, in particular, might support the decision to discontinue a drug. Nevertheless, larger controlled trials are needed to confirm the usefulness of this marker in daily clinical practice.

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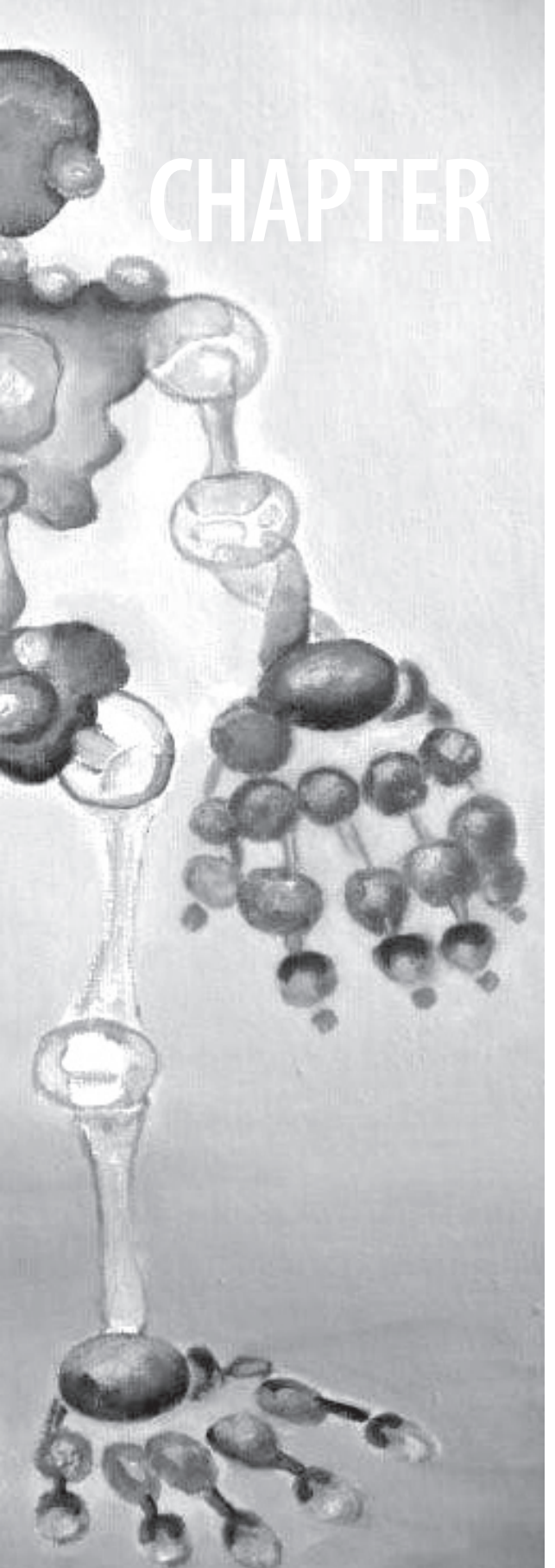

CHAPTER 7

General discussion

LESSONS LEARNED FROM THE DUTCH ABC REGISTER

The ABC register was set up in 2003 with inclusion of JIA patients treated with biologic agents since 1999. It was designed to evaluate the use, effectiveness and safety of biologic agents in JIA. The increasing number of patients considered for biologic therapy and the changing treatment strategies allowed us to evaluate the treatment responses in more detail, to describe specific subgroups of patients and to compare treatment strategies.

The lessons learned from the ABC register can be grouped in the following discussion subjects:

1. Effectiveness of etanercept and predicting treatment response

- In general, the treatment goal has shifted nowadays to the achievement of inactive disease with prevention of structural joint damage and functional decline.[Chapter 2.1]
- Among patients with JIA who initiated treatment with etanercept, one-third achieved an excellent response, one-third an intermediate response, and one-third a poor response to therapy.[Chapter 3.1]
- Achievement of an excellent response was associated with low baseline disability scores, fewer synthetic DMARDs used before etanercept and younger age at onset JIA, and achievement of a poor treatment response with systemic JIA and female gender. [Chapter 3.1]
- While a range of 37-49% of the patients reached inactive disease, only 15% of patients tried to discontinue etanercept eventually. Patients that stopped etanercept successfully after achievement of disease remission had an initial longer course with etanercept than patients who flared after discontinuation. [Chapter 3.1]
- A substantial proportion of patients who had not responded to etanercept at three months, responded later on, indicating a delayed treatment response.[Chapter 4.1]
- Patients with systemic JIA in general responded worse to treatment with etanercept, however also 24% of systemic patients achieved an excellent response. While systemic JIA is clearly distinguished from other JIA categories, differences exist within the category.[Chapter 3.1]
- The toll-like receptor 4 agonist MRP8 and MRP14 protein complex seems a sensitive indicator for disease activity and a predictor for relapses in systemic JIA.[Chapter 6]
- Etanercept is also considered in patients with the enthesitis related arthritis, psoriatic arthritis and oligo-articular persistent JIA categories. Patients grouped within these categories were as responsive and as tolerant to the introduced biologics compared

with JIA patients with poly-articular course or oligo-articular extended JIA.[Chapter 3.2-3.4]

2. Comparative effectiveness of biologic agents

- During the last decade, biologic agents are prescribed increasingly in daily care. [Chapter 5.1]
- The short-term efficacy of etanercept, adalimumab and abatacept seemed similar for poly-articular course JIA and the short-term efficacy of anakinra, canakinumab and tocilizumab similar for systemic JIA.[Chapter 2.2]
- During 12 years of treatment observation, etanercept remained first biologic treatment choice for poly-articular course JIA, while anakinra has become first choice for systemic JIA. [Chapter 5.1] Observed differences between etanercept and adalimumab treated patients mainly regarded the presence of uveitis.[Chapter 5.2]
- Around 20% of patients treated with etanercept as first agent switched to a second biologic. After etanercept failure, adalimumab and infliximab were equally effective in JIA patients with non-systemic JIA categories, while anakinra was superior to a second TNF-alpha blocking agent in systemic JIA. Overall, the effectiveness of a second biologic agent was lower than the first biologic and seems especially low when the first agent was discontinued because of primary ineffectiveness.[Chapter 4.2]

3. Timing of biologic treatment introduction

- Biologic agents are nowadays introduced earlier during the disease course and in patients with lower disease activity, which has resulted in better patient outcomes. [Chapter 5.1]
- Achievement of an excellent response was associated with low baseline disability scores and fewer DMARDs used before etanercept. Prevention of high disability and minimizing the use of multiple DMARDs before etanercept indicates that treating patients with biologic agents more early in the disease course is beneficial.[Chapter 3.1]

4. Monitoring of disease activity

- Because of a decreasing disease activity in all core set variables at baseline, the validity of the ACR paediatric response criteria needs to be re-evaluated. Especially the function of ESR, which nowadays is found to be within normal range for non-systemic JIA patients before introduction of biologic agents, might be questioned as no further improvement from normal could be expected.[Chapter 5.1]

5. Safety of biologic agents

- Etanercept was well tolerated, with a favourable safety profile for the short term and long term. However, development of de novo auto-immune diseases (like inflammatory bowel diseases, psoriatic skin lesions and sarcoidosis) has been reported during etanercept treatment. This paradoxical adverse event needs to be evaluated further. [Chapter 3.1, 3.2, 3.5]

In this chapter the above mentioned discussion subjects will be addressed in light of previously published studies. Furthermore the methodological considerations will be taken into account and this general discussion will conclude with implications for daily clinical care and indications for future research.

EFFECTIVENESS OF ETANERCEPT AND PREDICTING TREATMENT RESPONSE

The initial randomized controlled trial that evaluated the treatment efficacy of etanercept (the first approved biologic agent) in JIA, published in 2000, chose the achievement of an ACRpedi30 response as primary outcome.[1] As a result of the treatment successes gained during the last decade, the treatment goal has shifted nowadays to the achievement of inactive disease with prevention of structural joint damage and functional decline.

So far, over 85% of JIA patients included in the ABC register initiated etanercept as a first biologic agent. We showed that, 4 to 7 years after initiation of etanercept, in daily practice, a range of 37-49% of the patients had achieved inactive disease.[2] Some of these patients seem to have a delayed clinical response to etanercept.[3] This rate of inactive disease achieved with etanercept is comparable with the reported rates in the German etanercept registry and in the extended open-label trial by Lovell et al.[4-5] The percentage of patients that achieved inactive disease is high, especially considering the fact that these patients were previously unresponsive to conventional treatment including methotrexate. Disease remission off medication is the ultimate treatment goal. However, of all patients that initiated etanercept, only 9% of patients were able to discontinue etanercept successfully and retained disease remission.[2] Treatment still needs to be improved further.

The ability to identify patients who are more likely to respond to etanercept treatment would be an important step towards patient-specific treatment and subsequently could improve patient outcomes. We indicated factors associated with an excellent and a poor etanercept treatment response.[2] Achievement of an excellent response was associated with low baseline disability scores, fewer synthetic DMARDs used before etanercept and

younger age at onset JIA, and achievement of a poor treatment response with systemic JIA and female gender. A low baseline disability score and fewer synthetic DMARDs used prior to introduction of etanercept seem to indicate that earlier introduction might be associated with better treatment responses. The influence of timing is discussed later on. The remaining factors associated with better and worse treatment responses are possibly related to the patients' prognosis. It remains unknown whether patients with a poor response to etanercept would have responded better to other treatment options and further research is needed to clarify the understanding of these identified factors.
A combination of routine clinical data, levels of the biomarker MRP8/14, possibly accompanied by cytokine and genetic profiles, could eventually be useful in predicting which patients are likely to respond to treatment. The CHARM study indicated that higher levels of the biomarker MRP8/14 at baseline are associated with an excellent response to methotrexate treatment.[6] This biomarker also seems to indicate disease activity in systemic JIA and predict disease flares in patients with systemic JIA and in JIA patients after discontinuation of methotrexate.[7] The results of the MRP8/14 protein for the initial response to etanercept in all JIA categories (with contribution of data from the ABC register) are expected in 2012.

JIA is a heterogeneous disease with different patient and disease characteristics and varying clinical courses and responses to treatment. Identification of prognostic and predictive factors might eventually change the current classification of JIA.
Classification into the 7 JIA categories is currently based upon clinical and laboratory findings within the first 6 months after onset of JIA.[8] The aim of this International League of Associations for Rheumatology classification system was to identify homogeneous disease groups and some of these categories seem to represent well characterized groups of patients. Systemic JIA for example has already been considered by many as a different disease entity because of the differences in pathogenesis with involvement of the cytokines IL-1, IL-6, IL-18 and pro-inflammatory S100-proteins compared with oligo-articular and poly-articular JIA.[9] While systemic JIA is clearly distinguished from other JIA categories, differences exist within the category, with some systemic JIA patients having prominent systemic features and others a disease course with a destructive, invalidating poly-arthritis.[10] These differences within the systemic JIA category are reflected in our results; although systemic JIA was in general associated with a poor response, 24% of systemic JIA patients achieved an excellent response.[2] Other categories, like juvenile psoriatic arthritis (JPsA), seem to include more heterogeneous groups of patients. An evaluation of the JPsA patients from the ABC register has learned that some of these patients switched between JIA categories, most often because of a late onset of psoriatic skin lesions.[11] This is not surprising, because, in JPsA, the arthritis precedes psoriatic skin lesions in about 50% of the cases and psoriatic skin lesions may occur even years

after onset of arthritis.[12] A difference between, at onset, older JPsA children who are more likely to have features of spondylo-arthritis, and patients with early-onset JPsA who have a female predominance and ANA positivity has been reported.[13] Ravelli et al. recommended a different classification of the antinuclear antibody (ANA) positive patients since these patients reflect a more homogeneous subset of patients with regard to patient and disease characteristics, however, this is not adopted in clinical care.[14-15] Although the classification of JIA might change, it is important to evaluate the effectiveness of biologic agents in all JIA patients. The randomized controlled withdrawal trial that evaluated etanercept in JIA only included patients with the systemic, poly-articular (rheumatoid factor positive and negative) and oligo-articular extended categories.[1] However, in daily clinical practice, also patients with the JPsA, enthesitis related arthritis (ERA) and oligo-articular persistent categories receive etanercept treatment, and we therefore highlighted the effect of etanercept in patients with these categories.[11, 16] No studies have focussed on the effectiveness of etanercept in JPsA, and only a few case-series (mainly retrospective and with limited follow-up duration) explored the effectiveness of etanercept for patients with the ERA category.[17-19] The majority of JPsA patients eventually achieved inactive disease, and this percentage was substantially higher than seen in all JIA categories. Fewer patients with the ERA category achieved inactive disease and this did not seem to sustain in the few patients with a longer follow-up, as is also seen in adult-onset ankylosing spondylitis.[20-22] Furthermore, as more experience is gained with TNF-alpha blockers, some patients with refractory oligo-articular persistent JIA are considered for biologic therapy, even though it has not been approved for patients with an oligo-articular disease course. We showed that the disease activity declined rapidly after introduction of biologic treatment.[Chapter 3.4] It is interesting why some oligo-articular persistent JIA patients require biologic therapy and others not. Fewer patients were ANA positive and age at onset seemed to be older in this subset of oligo-articular persistent patients that require biologic therapy. This again underlines the fact that age at onset and ANA positivity could be used to identify a homogeneous subset of patients.

COMPARATIVE EFFECTIVENESS OF BIOLOGIC AGENTS

During the last decade the availability of biologic agents for the treatment of JIA increased substantially. Physicians involved in the treatment of JIA nowadays face this increasing number of biologic treatment options and because direct head-to-head trials comparing biologics are lacking, choosing between these treatments is often difficult.

We therefore conducted a systematic review and retrieved all available efficacy data from previously conducted trials.[Chapter 2.2] The efficacies of the biologics were, if similarity of trials was assumed, compared indirectly. For poly-articular course JIA (any JIA onset category), etanercept, adalimumab and abatacept seem equally efficacious in preventing disease flare after response to treatment. However, though no significant differences were found, some arguments might support the existence of differences in efficacy between these biologics and might indicate that etanercept and abatacept are superior to adalimumab. For systemic JIA, canakinumab, tocilizumab and anakinra seem to have a comparable effect. Canakinumab might favour tocilizumab, but this difference was not significant and more research is needed to confirm. However, these results need to be interpreted with care since trials seem to differ with regard to included patients. Because of lacking evidence, head-to-head trials evaluating different biologics directly are urgently needed.

In daily practice, etanercept seems to remain first choice for poly-articular course JIA, but adalimumab is preferred when uveitis is present or when an increased risk for the development of uveitis is expected.[23-24] For systemic JIA, a change in treatment strategy, with IL-1 and IL-6 blocking agents taking a more prominent place over TNF-alpha antagonists, is seen. 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, including studies from the ABC register, do indicate that etanercept is effective in some systemic JIA patients.[2, 25-26] Many observational studies found anakinra to be highly effective [27-28], but observational studies that evaluate canakinumab and tocilizumab in systemic JIA are still lacking. The ACR 2011 recommendations distinguish patients with systemic JIA and presence of systemic features, for which anakinra is first choice, from patients with systemic JIA and active arthritis, for which or anakinra or TNF-alpha antagonists is suggested.[29] These recommendations provide a useful tool, however, since new treatments are being developed rapidly, these recommendations are already dated and inclusion of the IL-6 receptor antagonist tocilizumab (approved by the FDA for systemic JIA in April 2011) is omitted, as are the IL-1 inhibitors canakinumab and rilonacept. This emphasizes the importance of an ongoing evaluation of current treatments in JIA.

After failure to etanercept, the effectiveness of a second introduced biologic agent has been evaluated. Adalimumab and infliximab were equally effective in JIA patients with non-systemic JIA categories who failed on etanercept treatment. For systemic JIA, anakinra was superior to a second TNF-alpha blocking agent. Furthermore, patients who switched to a second biologic with uveitis as reason all switched to adalimumab. [Chapter 4.2] This was the second study that evaluated the effectiveness of switching in

JIA in detail. Tynjala et al. described a switch between etanercept and infliximab, while our study with data from the ABC register described mainly a switch from etanercept to adalimumab in the non-systemic JIA categories and a switch from etanercept to anakinra in systemic JIA.[30] The observed switching patterns are inevitable influenced by the availability of biologic agents within the study period in the Netherlands. We could conclude that switching to a second biologic agent in JIA occurs frequently in daily practice and seems to be a safe option for JIA patients who failed etanercept.

Until conclusive differences are established, decisions to choose between biologics in JIA should mainly depend on drug availability, safety (including available data on long-term safety), practical reasons (like interval of injections), and treatment costs. Furthermore, more insight in other features than clinical characteristics, such as cytokine or genetic profiling and biomarkers, related to the treatment response might contribute to this decision making.

TIMING OF BIOLOGIC TREATMENT INDUCTION

In rheumatoid arthritis (RA), the existence of a "window of opportunity" early in the disease course when treatment is more likely to succeed than when the same treatment was applied later on, has been first described in 1989.[31] Since then, many studies in RA comparing different treatment strategies have demonstrated advantages of early aggressive therapy in terms of prevention of radiological damage after years.[32-34]
The observation that the achievement of better outcomes was related with earlier introduction of treatment has also been reported for JIA patients treated with methotrexate and sulfasalazine.[35-36] The PRINTO group analyzed factors associated with poor response to methotrexate treatment in JIA patients and found, among others, an association with longer disease duration and higher disability scores.[37] Using data from the ABC register, we found that an excellent response to etanercept was associated with lower disability scores and fewer DMARDs used before the introduction of etanercept.[2] All these results show that the treatment strategy is important for both RA and JIA. So far, 2 clinical trials have compared different early aggressive induction regimens in JIA patients and both confirmed the benefits of early aggressive treatment as early as 6 months after initiation. The TREAT trial (double-blind, placebo-controlled) compared high dose parental methotrexate, etanercept and 4 months of tapered prednisone with high dose parental methotrexate and etanercept placebo and prednisone placebo in early poly-articular JIA patients.[38] There seemed to be a trend towards a higher rate of inactive disease in the more aggressive treatment arm (40% compared with 23% of patients), however, no significance was reached. They did find an association between shorter disease dura-

tion at baseline and higher chance of achieving inactive disease after 6 months.[38] The ACUTE-JIA open-label trial included DMARD-naïve patients with persistent poly-arthritis and compared 3 treatment induction strategies.[39] An ACRpedi75 response was more often reached in patients enrolled in the aggressive group (100% for infliximab plus methotrexate vs. 65% and 50% for synthetic DMARD only groups).[39] It is reassuring that in both trials no differences in short-term safety profiles were seen.[38-39]

This early aggressive treatment approach is also adapted in daily clinical care. Analyzing the data included in the ABC register per calendar-year of biologic treatment induction, allowed us to distinguish a trend towards prescription of biologic agents in patients with, at baseline, shorter disease duration and lower disease activity (including less joints with arthritis, lower CHAQ scores).[Chapter 5.1]

However, not all patients should be treated early aggressively considering the fact that biologic agents might have long-term serious adverse effects and accompany high costs. Therefore only those patients who are most likely to develop a severe disease course should receive early aggressive treatment, and unnecessary exposure to biologic agents should be avoided.

MONITORING OF THE DISEASE

Since 1997 the validated ACR paediatric criteria have been used internationally to evaluate the response to therapy in JIA.[40] These response criteria reflect the percentage of improvement in 6 "core set" variables compared with baseline values. These criteria have been validated in JIA patients with a poly-articular disease only. The "core set" variables include the physicians' global assessment of disease activity, CHAQ score, global assessment of wellbeing by parent/patient, number of active joints with arthritis and joints limited in motion and ESR value. Because the patient population considered for biologic therapy is changing towards a less severely affected population with fewer joints with arthritis, lower CHAQ scores, lower number of joints with limited motion and lower ESR values at start of biologic treatment, improvement in all of these variables might be less evident and an ACR paediatric response might therefore be less accurate. [Chapter 5.1] New measurements to evaluate treatment responses for these patients are needed. Recently, the Juvenile Arthritis Disease Activity Score (JADAS), providing a one number summary on a continuous scale, has been developed and reflects the disease activity at a certain point in time, not related to baseline.[41] Cut-off points for disease remission, minimal disease activity and acceptable symptom state were determined and validated.[42] These cut-off points may, if applied regularly in daily clinical care, allow tighter control of treatment and help decision making. In early RA, a disease activity score (DAS)-driven tight treatment strategy that aimed at a score below a certain cut-off

point resulted in higher percentages of remission which were also achieved earlier than usual care.[43-45] The effect of tight treatment control strategy is still not evaluated in JIA.

SAFETY OF BIOLOGICS

The safety of etanercept and other biologic agents remains an important topic. Etanercept was overall well tolerated by the patients included in the ABC register. Unfortunately, no safety profile of other biologic agents for its use in JIA could be given because, until now, insufficient patient-years of exposure to those drugs are observed in the Netherlands. The safety profiles of etanercept (0.05 serious adverse events (SAEs) per patient-year of exposure) were comparable with the open-label extension trial data (0.12 SAEs per patient-year), and with the German etanercept register (0.02 SAEs per patient-year).[2, 4-5] Also for the specific JIA categories JPsA, ERA and oligo-articular persistent JIA, comparable SAE-rates were seen, however, the number of patients with these specific JIA categories included was low.[11, 16] The greatest safety concerns regard severe infections requiring hospitalization, the development of other auto-immune diseases and the development of malignancies.[2]

Infections

The observed rate of infections in the ABC register was 14 infectious AEs and 1 serious infection per 100 patient-years of etanercept exposure. In the literature, this rate varies between the clinical trials and observational registries.[46] Overall, around 1-3 serious infections per 100 patient-years of exposure have been reported, which is similar to the rate observed in the ABC register. The German registry found an increased risk for infectious SAEs for etanercept with methotrexate therapy compared to mono-therapy etanercept.[47] It is reassuring that a recent cohort study that included over 10,000 patients with RA found no difference in the occurrence of serious infections that required hospitalization between patients treated with TNF-alpha antagonists and comparator regimens (synthetic DMARDs). They did find an increased risk for RA patients treated with infliximab and adalimumab compared with etanercept.[48]

Autoimmune phenomena

The occurrence of autoimmune phenomena during biologic treatment has been reported in RA and JIA patients.[49-51] Also in the ABC register development of Morbus Crohn, colitis ulcerosa, sarcoidosis, psoriatic skin lesions, uveitis, multiple sclerosis-like symptoms and interstitial lung disease during etanercept treatment has been observed.[2, 11] This development of other auto-immune diseases during biologic treatment is rare and its cause is still a matter of debate. It could be an adverse event of the biologic treat-

ment; however, it could also be due to a higher prevalence of combined auto-immune diseases because of common etiological and/or genetic mechanisms. Kappelman et al. found that children with IBD were more likely to have co-morbid auto-immune diseases (RA, SLE, hypothyroidism and diabetes) compared with healthy matched controls, irrespective of treatment with TNF-blockers.[52]

Malignancies

A total of 48 paediatric cases of malignancies during anti-TNF-alpha treatment have been reported by the FDA, of which 15 during etanercept treatment.[53] It remains unknown whether there is a causal relationship between TNF-alpha antagonists and the development of malignancies, or whether this potential higher rate of malignancies is caused by the use of other immunosuppressive drugs, or explained by an increased background rate for malignancies in severely affected JIA patients. For RA patients many reviews have tried to enlighten the concerns with regard to an increased malignancy risk, and the majority of meta-analyses conducted so far show no increased risk.[54-57] A Swedish matched case-control study found a substantially increased risk for lymphoma, only in those RA patients with very severe disease. They concluded that high inflammatory activity, rather than its treatment, is a major risk factor.[58] It is reassuring that, until now, no malignancies have been reported in our register which currently covers over 1,000 patient-years of follow-up since introduction of etanercept.

To elucidate these safety concerns, large cohorts of patients followed for decades are essential. Reference data for children with auto-immune disease treated with immunosuppressive medications are required to allow for accurate comparisons. The propensity score matching strategy could be considered.[59] This strategy allows matching controls with regard to the probability of exposure of a certain treatment of interest and therefore adjusts for potential confounding factors like severity of disease.

METHODOLOGICAL CONSIDERATIONS AND CHALLENGES OF OBSERVATIONAL COHORT STUDIES

The studies described in this thesis have mainly been conducted with data from the Dutch national ABC register. As with all prospective observational cohort studies, this study is prone to some biases which need to be considered carefully before interpreting the results. Discussion of the biases, methods to (partially) account for its consequences and challenges is essential and strengthens the report of epidemiological studies.

To evaluate the effectiveness of a certain drug, a randomized placebo controlled trial is the design of first choice. Because a randomized controlled trial compares two, in definition, identical patient groups, results are automatically corrected for potential known and unknown confounding factors (a confounding factor may mask or falsely demonstrate an association). In paediatric rheumatology the randomized placebo-controlled withdrawal design is mainly used and includes an open-label lead-in phase, where all patients receive the drug, followed by a placebo-controlled phase, where only those patients who had responded are randomized. As discussed in Chapter 2.2, this design has several limitations. Instead of an estimation of the initial response to the treatment, the effect of treatment discontinuation has been researched. Better protection of flares after primary response does not necessarily imply better initial treatment responses.
A trial is not suitable to evaluate long-term effects years after initiation of the drug in a non-selected large patient population due to practical, financial and ethical reasons. Therefore, to evaluate the long-term effects, prospective observational studies were set-up, of which the ABC register is an example.
The main strength of the ABC Register is that, since the introduction of etanercept in 1999, all JIA patients who initiated a biologic agent in The Netherlands are included and no selection bias occurred. Patients enrolled in randomized clinical trials had to be excluded because of competing interests, nevertheless, for completeness, the number of patients involved in trials have been reported. This prospective observational design evaluates a non-selected patient population in a real-life setting. However, compared to the placebo-controlled trials, no control group was available. In fact, it is impossible to select a proper control group, because patients with JIA not treated with biologic agents represent a different patient group with different patient and disease characteristics and prognosis. Yet, because no control group was available, it is important to realize that a part of the reported treatment effectiveness could be subject to confounding factors, like the natural course of the disease. For the results evaluating factors associated with treatment response, it is impossible to indicate whether these factors are associated with the response to etanercept in specific, or reflect overall prognostic factors. Furthermore, it remains unknown whether patients would have responded better to other treatment options.

Until now over 400 JIA patients have been included in the register. During the observed 12 years of biologic treatment in JIA, new insights have been gained and differences in treatment strategies are known to exist. JIA is a heterogeneous disease, and together with the fact that the population considered for biologic therapy is changing (i.e. less severely affected), the results of the studies discussed reflect a heterogeneous group of JIA patients. Unfortunately, statistical power was too low to correct for all of these differences.

In this thesis 3 case-series of patients with the psoriatic arthritis, enthesitis related arthritis and oligo-articular persistent JIA categories have been reported separately. Nonetheless, because of the low number of patients included these results should be interpreted with care.

In this long-term study, paediatric rheumatologists approximately enter study data twice a year for each patient they treat with biologic agents. More and more patients are considered to start using biologic agents and this requires a large commitment of these physicians. Even though data entry is easily accessible (web-based) and kept to a minimum, delayed data entries are inevitable. Because of this way of data collection, missing values are also more prone to occur. Around 10-15% of the JIA core set variables were missing in the register, this mainly applied to the physician's global assessment of disease activity score, CHAQ score, and global assessment of wellbeing score. The JIA core set consists of 6 variables, all indicating the disease activity at a certain point in time. If no more than 3 of these 6 variables were missing, these missing values were imputed in a multivariable regression model to estimate the underlying distribution of the missing value in the source population based on the other known variables of the subject. Multiple imputation is a valid method, especially since the missing data in the ABC register are thought to be either missing completely at random or missing at random dependent on the remaining values of the JIA core set (of which at least 3 need to be present before imputation occurred).

Due to the ongoing design, the total follow-up duration varied between patients and introduced some challenges. The use of a survival analysis is an elegant way to account for this difference in follow-up duration and only those patients still at risk for an event are evaluated. Drug survival (or drug continuation, censored for treatment discontinuation because of disease remission) was used multiple times as a proxy of treatment response. Though drug survival is associated with treatment response, it is also related to other independent factors, such as the availability of other drugs and absence of further treatment options. Most likely a more accurate way to evaluate treatment response is to use the ACR paediatric response criteria. This comes with some challenges, because patients have varying follow-up durations, the fulfilment of these response criteria differs during follow-up, and patients discontinue treatment. The use of an intention-to-treat method (i.e. inclusion of all patients that had ever initiated the agent independent of any treatment changes thereafter) prevents the fact that only those patients that remain on the drug are analyzed and thereby avoids reflecting the good responding group only. However, the intention-to-treat analysis could overestimate the reported effectiveness since the responses to other treatments started or changed during the follow-up period will also be reflected. This also includes the use of concomitant medications. Because

this is a real-life setting, no restrictions regarding its use were applied. For the short-term the influence of concomitant medications is thought to be minimal, and a description of the discontinuation of concomitant agents (like systemic prednisone and methotrexate) has been used as a marker for treatment success.
Drug survival seems to be more specific for the drug studied, and the results of the intention-to-treat analyses seem to report the overall outcomes of patients that are considered for biologic treatment and reflect current treatment strategies. The use of a combination of both of these treatment outcomes have been opted and is called the LUNDEX procedure.[60] In this procedure the outcome at a certain time point T is adjusted for the percentage of patients still on the drug at time T. This method is used in Chapter 5.1 and should be used more often in the evaluation of treatment responses for JIA patients in observational data to allow for comparing.

While the mentioned biases need to be taken into account when interpreting the results, and, where possible, need to be prevented or corrected for, this prospective observational cohort study is ideal to compare different outcomes of treatments, disease courses, and occurrence of adverse events during (multiple) treatments over long periods of time.

IMPLICATIONS FOR DAILY CLINICAL CARE

We can conclude that the use of etanercept is effective and safe for all patients with non-systemic JIA categories. Clinical remission has become a reachable treatment goal. For these JIA patients, etanercept, adalimumab and abatacept seemed equally effective in preventing a disease flare when comparing the randomized controlled withdrawal trial data indirectly. During 12 years of treatment observation, etanercept remained first biologic treatment choice for the non-systemic JIA patients. The presence of uveitis or an increased risk for the development of uveitis directed most physicians towards prescription of adalimumab. Prevention of high disability and minimizing the use of multiple DMARDs before etanercept indicates that treating patients with etanercept more early in the disease course could be beneficial. If a partial response after 3 months of etanercept treatment is observed, continuation until at least 6 months of treatment is recommended, because a delayed clinical response in a substantial proportion of patients was seen. After etanercept failure, the continuation rates for adalimumab and infliximab were similar.

Patients with systemic JIA in general responded worse to treatment with etanercept, however also 24% of systemic patients achieved an excellent response. While systemic

JIA is clearly distinguished from other JIA categories, differences exist within the category. Since 2008, anakinra has become first choice for systemic JIA in daily care. The short-term efficacy of anakinra, canakinumab and tocilizumab was similar for systemic JIA, but no comparisons with TNF-alpha blocking agents could be made. After etanercept failure, anakinra was superior to a second TNF-alpha blocking agent in systemic JIA. The place of tocilizumab and rilonacept in biologic treatment algorithms for systemic JIA still needs to be determined.

FUTURE RESEARCH

Despite the discussed progresses that resulted in an increased insight in biologic treatment responses in JIA, still many problems need to be solved. The ultimate treatment goal is disease remission off medication for all JIA patients, which so far is reached in only a minority of patients. Eventually we should aim for a normalization of the immune balance with restoring the physiological responses instead of suppressing the immune system.

First of all it is crucial to further understand the biologic and immunological pathways involved in the development of chronic arthritis. This may result in more effective and safer treatment options. In the future, some of the new drugs that are under investigation for RA could also be suitable for the treatment of JIA, and more agents are likely to be discovered. Each step of the treatment approaches needs to be evaluated in detail and optimization of these strategies with adoption of new agents is an ongoing process. The timing of the introduction of biologic treatment has to remain an important topic to be studied. However, early aggressive treatment also results in an increasing exposure to biologic agents, and a balance between the benefits of (early introduction of) biologic agents and its risk for adverse events needs to be researched. More research is needed to identify a risk profile and tailor treatment to each individual patient, and needs to include large patient groups and combine clinical, immunological (biomarkers) and genetic data.

Besides these studies evaluating initial treatment strategies, treatment stopping strategies in case of disease remission and switching strategies in case of treatment failure are also needed. Stopping and switching treatment should also be directed to each individual patient and should include the best treatment choices, so that the most optimal result can reached. Efforts to evaluate stopping strategies have been made in the Netherlands (ABC-STOP clinical trial) as well as the United States. The results are still expected. Hopefully, the results will guide effective and safe stopping strategies after

achievement of disease remission. Additional questions as how to diagnose silent subclinical arthritis are of importance and still unanswered. Initiatives to directly compare biologic agents in head-to-head trials are still lacking. Because up to 20% of patients require a second biologic agent and indirect treatment comparisons are limited because of great variances between separate trials, these head-to-head trials are urgently needed. More insight in reasons why some patients fail to biologic agents and others do respond needs to be gained.

National and international registries remain of great importance to evaluate daily patient care. These registries provide a real-life picture of patients and can easily provide answers to questions derived from daily clinical practice and are an ongoing source of data. Large JIA patient populations followed into adulthood are needed to investigate rare adverse events like the development of other auto-immune disorders and malignancies. Initiatives to combine registries have begun in Europe and the United States and should help answer questions on the long term safety of biologic agents. These initiatives will also generate more possibilities to perform subgroup analyses. Furthermore, studies comparing different treatment strategies including different introduction stopping and switching strategies will provide large amounts of information and will help to optimize tailored patient specific treatment.

Hopefully, these efforts will result in more effective and safer drugs, better monitoring of disease activity, optimal treatment strategies with a more tailored patient specific approach and finally will improve the outcomes of JIA patients.

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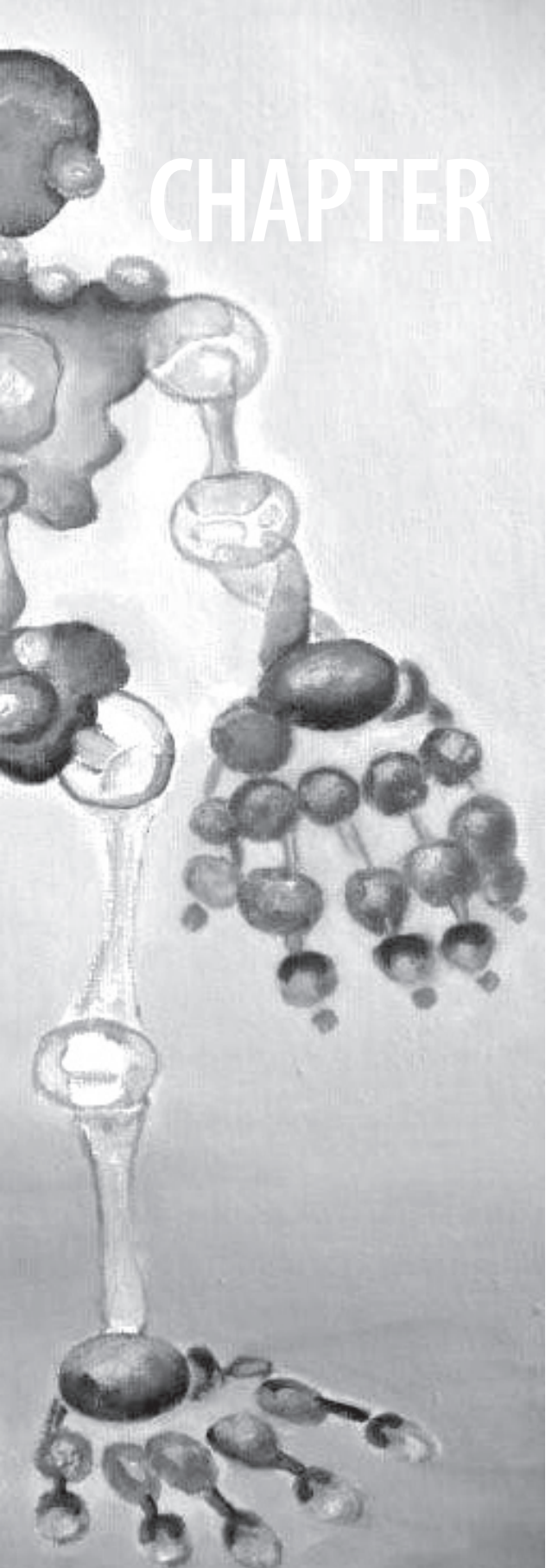


CHAPTER 8

English Summary/ Nederlandse Samenvatting

ENGLISH SUMMARY

Chapter 1 provides information on the design of the ABC register and the aims of this thesis that includes to evaluate and compare the effectiveness of all biologic agents used in JIA and to gain further insight in the response and safety to etanercept treatment.
In Chapter 2, the literature of JIA and biologic treatment has been evaluated. Chapter 2.1 gives an overview of the diagnosis and management of JIA and describes in more detail the place biologic agents take in current treatment strategies. In this review a simplified approach to the current treatment of JIA is given and should advocate "tight" clinical control. Early recognition and early aggressive treatment of JIA prevents joint damage and allow for normal development and growth. For JIA patients with an oligo-articular or poly-articular course, TNF-alpha antagonists are indicated after failure of NSAIDs, intra-articular steroids and sDMARDs including methotrexate. The treatment of systemic disease is challenging. Different cytokine profiles (IL-1 and IL-6) seem to underlie systemic JIA and a change in treatment strategy, with anakinra (IL-1 blockade) taking a more prominent place over TNF-alpha antagonists, is seen. Today, most experts favour anakinra when systemic features are prominent, but the timing of this treatment is debatable.
These treatment regimens for poly-articular course JIA and systemic JIA are based on a few randomized clinical trials each comparing 1 agent and observational studies. Randomized controlled trials comparing different biologic agents directly are until now lacking. In Chapter 2.2 an effort to compare the clinical trials indirectly was conducted. Because the trials differed significantly with regard to design (withdrawal design versus "classic" randomized controlled trial) and patients' characteristics (mainly disease duration and included JIA categories), efficacy could be compared indirectly for only a subset of agents. An overview of the quality of the conducted trials is given and the short-term efficacy seemed similar across biologic agents (etanercept, adalimumab and abatacept) for poly-articular course JIA. For systemic JIA, anakinra, canakinumab, tocilizumab were found equally effective. Because of the observed differences between trials, head-to-head trials comparing 2 biologic agents directly are highly needed. 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.

In Chapter 3 the long-term effectiveness and safety of biologic agents in a previously biologically-naive Dutch JIA population is evaluated. Among patients with JIA who initiated treatment with etanercept, one-third achieved an excellent response, one-third an intermediate response, and one-third a poor response after 15 months of treatment. After 51 months of treatment, 40% (95% CI 26%-54%) achieved a state of inactive dis-

ease. While this percentage is high and impressive, the ultimate goal to achieve inactive disease by all patients is still not reached and treatment strategies need to be improved further more. By analyzing factors associated with etanercept treatment response, we have gained more insight on how to further improve the patients' outcomes. Achievement of an excellent response was associated with low baseline disability scores, fewer DMARDs used before etanercept and younger age at onset JIA, and achievement of a poor treatment response with systemic JIA and female gender. While these factors are mainly prognostic, prevention of high disability and minimizing the use of multiple DMARDs before etanercept indicates that treating patients with biologic agents more early in the disease course is beneficial. The outcomes of systemic JIA patients treated with etanercept were less impressive, and the median time on drug before discontinuation due to ineffectiveness or intolerance was shorter than for the non-systemic categories. However, still a proportion of systemic JIA patients (24%) did respond to etanercept and achieved inactive disease.(Chapter 3.1)

In more detail, the responses of TNF-alpha antagonists in the enthesitis-related arthritis, psoriatic arthritis and oligo-articular persistent categories were described (Chapter 3.2, 3.3 and 3.4). Although all available TNF-blocking agents were prescribed in patients classified into these 3 categories, most patients started etanercept, and these results therefore mainly reflect the effectiveness of etanercept. Patients with enthesitis-related arthritis, psoriatic arthritis and oligo-articular persistent JIA responded very well after as early as 3 months of treatment. Evaluation of these patients has learned that etanercept is a justifiable treatment option for patients with enthesitis-related arthritis and psoriatic arthritis who previously did not responded to methotrexate, and for oligo-persistent JIA patients when treatment with intra-articular corticosteroid injections and methotrexate has failed.

Etanercept was well tolerated, with a favourable safety profile as is revealed by a low serious adverse event rate (0.05 per patient-year of exposure). The safety profiles for patients with the enthesitis-related arthritis, psoriatic arthritis and oligo-articular persistent JIA categories were comparable. Safety of etanercept (and other biologic agents) remains an important topic. No malignancies have been reported in the ABC Register. However, development of *de novo* auto-immune diseases (like inflammatory bowel diseases, psoriatic skin lesions and sarcoidosis) has been reported during etanercept treatment. Whether there is a causal relation to etanercept is unclear; it could be a paradoxical adverse event, a late-onset manifestation that could have resulted in a wrong diagnosis, or a coincidental combination. No safety profile of other biologic agents for its use in JIA patients could be given because until now too few patient-years of exposure with those drugs have been observed in the Netherlands.

Furthermore we have evaluated the long-term effects of etanercept on the growth and bone status in a subset of patients included in the ABC Register between 2003 and 2010

(Chapter 3.5). We concluded that low linear height and low bone mineral density (for height adjusted) seemed to be infrequent in JIA patients that qualify for etanercept treatment nowadays. In contrast to previous reports, no improvements in height and bone status during etanercept treatment were seen.

Different treatment approaches after failure of etanercept in JIA have been described in Chapter 4. Chapter 4.1 illustrates a delayed clinical response in a substantial proportion of patients (55%) that previously did not responded to etanercept at three months. We concluded that, especially in patients with a partial initial response, continuation of treatment to at least six months is recommended. Chapter 4.2 reports on switching between biologic agents. Around 20% of patients treated with etanercept as first agent switched to a second biologic agent. After etanercept failure, adalimumab and infliximab were equally effective in JIA patients with non-systemic JIA categories, while anakinra was superior to a second TNF-alpha blocking agent in systemic JIA. Overall, the effectiveness of a second biologic agent was lower than the first biologic and seems especially low when the first agent was discontinued because of primary ineffectiveness. We concluded that switching between biologic agents seems to be safe and, since limited options are available, justifiable for JIA patients who failed etanercept.

Since over 12 years of biologic treatment observation in the Dutch national ABC register is included, and during this period new agents and new insights in treatment approaches are gained, differences in the prescription of biologic agents are presented in Chapter 5. Chapter 5.1 describes that biologics are nowadays being prescribed increasingly and earlier during the disease course. JIA patients taken into consideration for first biologic treatment changed towards a less severely affected population which is subsequently accompanied by better short-term disease outcomes. While etanercept remained biologic of first choice for JIA patients with non-systemic JIA categories, anakinra has become first choice for systemic JIA patients. In Chapter 5.2 the differences between the etanercept and adalimumab treated patient groups are highlighted. Patients to whom adalimumab was prescribed were characterised by a history of uveitis, longer disease duration and lower disease activity as compared with the etanercept treated patients. In a qualitative focus group analysis, the presence of uveitis was acknowledged by the interviewed physicians to be one of the most important factors that directed their choice towards adalimumab. More extensive experience with and more existing scientific evidence for etanercept and the painful adalimumab injections were the most important reasons to be reticent with the prescription of adalimumab.

In the addendum (Chapter 6), the results of an international collaboration that collected serum samples of systemic JIA patients treated with synthetic DMARDs and biologic

agents, are presented. This international research group has evaluated the values of a specific biomarker (i.e. toll-like receptor 4 agonist MRP8 and MRP14 protein complex) and found it to be a sensitive indicator for disease activity and a predictor for relapses in systemic JIA.

This thesis ends with a general discussion described in Chapter 7. The different lessons learned from this thesis are highlighted and addressed in light of previously published studies. Furthermore the methodological considerations are taken into account and the implications for daily clinical care and the indications for future research are discussed.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 beschrijft het ontstaan en de opzet van het ABC register en de doelstellingen van dit proefschrift. Deze doelstellingen omvatten het evalueren en vergelijken van de effectiviteit van de gebruikte biologicals bij kinderen met juveniele idiopathische artritis (JIA, of wel jeugdreuma) en het verkrijgen van meer inzicht in de respons op, en veiligheid van de behandeling met etanercept.

In Hoofdstuk 2 wordt achtergrondinformatie over de aandoening JIA gegeven en de behandeling met biologicals geëvalueerd. Hoofdstuk 2.1 beschrijft de aandoening JIA, wat als een paraplu-diagnose beschreven wordt en bestaat uit verschillende JIA categorieën. JIA wordt in de volgende categorieën opgedeeld: systemisch JIA (artritis gepaard gaand met systemische verschijnselen zoals koorts) en de niet-systemische JIA categorieën, welke bestaan uit poly-articulair JIA (reumafactor positief en negatief), oligo-articulair JIA (persisterend en uitbreidend), artritis psoriatica, entesitis gerelateerde artritis en ongedifferentieerde artritis. Verder schetst hoofdstuk 2.1 de verschillende overwegingen voor het stellen van de diagnose JIA en worden de behandelingsmogelijkheden en hierbij de plek die de behandeling met biologicals in de huidige behandelstrategieën heeft ingenomen, beschreven. In dit hoofdstuk wordt een vereenvoudigde en stapsgewijze benadering van de huidige behandeling voorgelegd. Deze benadering vereist regelmatige controle en, bij geen of onvoldoende respons, een snelle overgang naar de volgende behandelingsstap ("tight control"). Vroege herkenning en vroegtijdige agressieve behandeling van JIA voorkomt gewrichtsschade en maakt normale ontwikkeling en groei van het kind mogelijk. JIA patiënten met een oligo-articulair of poly-articulair ziektebeloop komen in aanmerking voor TNF-alfa antagonisten nadat er onvoldoende respons op de behandeling met NSAIDs, intra-articulaire steroïden en ziekte modificerende anti-reumatische middelen (DMARDs genoemd, waaronder methotrexaat) is behaald. De behandeling van systemisch JIA blijft een uitdaging. Verschillende cytokine profielen (IL-1 en IL-6 naast TNF-alfa) lijken ten grondslag te liggen aan de pathofysiologie van het systemische subtype en een verandering in de behandeling strategie waarin anakinra (IL-1 blokkade) een prominentere plaats heeft gekregen, wordt gezien. Tegenwoordig geven de meeste experts de voorkeur aan behandeling met anakinra wanneer er systemische kenmerken aanwezig zijn, maar de timing van deze behandeling blijft onbekend.
De beschreven behandelingen met biologicals voor JIA patiënten met een poly-articulair ziektebeloop en JIA patiënten met het systemische subtype zijn voornamelijk gebaseerd op een aantal gerandomiseerde klinische trials (elke trial vergelijkt 1 biological met placebo) en observationele studies. Gerandomiseerde klinische trials die verschillende biologicals direct met elkaar vergelijken zijn tot op heden niet verricht. In Hoofdstuk

2.2 wordt er een overzicht van de kwaliteit van de uitgevoerde trials gegeven en een poging ondernomen om de verrichte gerandomiseerde klinische trials indirect met elkaar te vergelijken. Deze trials verschilden in belangrijke mate met betrekking tot de opzet van de trials (een "withdrawal" opzet met een inductie fase versus een "klassieke" placebo-gecontroleerde en gerandomiseerde trial) en patiëntkarakteristieken (voornamelijk ziekteduur en geïncludeerde JIA categorieën). Door deze verschillen tussen de trials kon de effectiviteit slechts voor een deel van de biologicals worden vergeleken. De korte termijn effectiviteit leek vergelijkbaar voor de biologicals etanercept, adalimumab en abatacept bij JIA patiënten met een poly-articulair ziektebeloop. Bij systemische JIA patiënten werden de biologicals anakinra, canakinumab en tocilizumab even effectief bevonden. Door de waargenomen verschillen tussen de trials, blijft het verrichten van "head-to-head" trials die biologicals direct vergelijken noodzakelijk. Totdat deze trials verricht zijn, zal de kinderreumatoloog de keuze tussen biologicals moeten baseren op deze indirecte vergelijkingen aangevuld met observationele data afkomstig uit cohort studies en het in overweging nemen van de veiligheid en praktische en financiële argumenten.

In hoofdstuk 3 wordt de lange termijn effectiviteit en veiligheid van biologicals bij de Nederlandse JIA populatie die voor het eerst in aanmerking komt voor deze groep aan medicijnen geëvalueerd. Van de patiënten met JIA die startten met etanercept therapie, behaalde een derde een uitstekende respons, een derde een gemiddelde respons, en een derde een slechte respons na 15 maanden behandeling. Na 51 maanden behandeling, bereikte 40% (95% CI 26%-54%) inactieve ziekte. Terwijl dit percentage hoog en indrukwekkend is, wordt het uiteindelijke doel, het bereiken van inactieve ziekte, nog niet door alle patiënten bereikt en dienen de huidige behandelingsstrategieën verder te worden verbeterd. Door het analyseren van factoren die geassocieerd zijn met de respons op etanercept, hebben we meer inzicht verkregen in de wijze waarop een verdere verbetering van de uiteindelijke prognose van de patiënt kan worden behaald. Het bereiken van een uitstekende respons werd in verband gebracht met minder lichamelijke beperkingen en het gebruik van minder DMARDs voor de introductie van etanercept en een jongere leeftijd bij de diagnose JIA. Het bereiken van een slechte respons op de behandeling werd geassocieerd met het systemische subtype en het vrouwelijke geslacht. Hoewel deze factoren vooral prognostisch van aard zijn, geeft het voorkomen van lichamelijke beperkingen en het beperken van het aantal DMARDs voor behandeling met etanercept aan dat behandeling met biologicals eerder in het ziektebeloop gunstig is. De uitkomsten van systemische JIA patiënten behandeld met etanercept waren minder indrukwekkend, en deze systemische patiënten staakten etanercept als gevolg van ineffectiviteit of intolerantie eerder dan de overige niet-systemische categorieën. Echter, een deel van de systemische JIA patiënten (24%) respondeerden wel op

de etanercept behandeling en bereikten uiteindelijk inactieve ziekte. (Hoofdstuk 3.1) In de Hoofdstukken 3.2, 3.3 en 3.4 wordt de effectiviteit van TNF-alfa antagonisten bij patiënten met entesitis-gerelateerde artritis, artritis psoriatica en persisterende oligo-articulaire JIA in detail beschreven. Hoewel alle beschikbare TNF-alfa antagonisten werden voorgeschreven aan patiënten ingedeeld in deze 3 categorieën, startten de meeste patiënten met etanercept en de resultaten geven hierdoor voornamelijk de effectiviteit van etanercept weer. Patiënten met entesitis-gerelateerde artritis, artritis psoriatica en persisterende oligo-articulaire JIA reageerden over het algemeen uitstekend na 3 maanden behandeling. De evaluatie van deze patiënten heeft ons geleerd dat etanercept een gerechtvaardigde behandelingsoptie is voor patiënten met entesitis-gerelateerde artritis en artritis psoriatica die eerder niet reageerden op methotrexaat, en voor persisterende oligo-articulaire JIA patiënten wanneer de behandeling met intra-articulaire injecties met corticosteroïden en methotrexaat heeft gefaald. Etanercept werd over het algemeen goed verdragen zoals blijkt uit een gunstig veiligheidsprofiel met een lage incidentie van ernstige bijwerkingen (0.05 SAEs per patiënt-jaar). De veiligheidsprofielen voor patiënten met de categorieën enthesitis-gerelateerde artritis, artritis psoriatica en persisterende oligo-articulaire waren vergelijkbaar. Veiligheid van etanercept (en andere biologicals) blijft een belangrijk onderwerp. Tot dusverre zijn er geen maligniteiten in het ABC register gemeld. Echter, ontwikkeling van de novo auto-immuunziekten (zoals inflammatoire darmziekten, psoriatische huidlaesies en sarcoïdose) werd wel tijdens de behandeling met etanercept gemeld. Het is nog onduidelijk of er een causaal verband met etanercept bestaat, of dat er mogelijk sprake is van een late manifestatie van de extra-articulaire kenmerken, of ontwikkeling van een andere auto-immuun ziekte. Er kan geen veiligheidsprofiel van de andere geëvalueerde biologicals worden gegeven, omdat er tot nu toe te weinig patiënt-jaren tijdens blootstelling aan deze medicijnen zijn waargenomen in Nederland. Tevens zijn de lange termijn effecten van etanercept op de groei en de botdichtheid in een subgroep van patiënten uit het ABC register geëvalueerd (hoofdstuk 3.5). We concludeerden dat kleine lichaamslengte en lage botdichtheid (gecorrigeerd voor de lichaamslengte) weinig voorkomen bij JIA patiënten die in aanmerking komen voor etanercept behandeling tussen 2003 en 2010. In tegenstelling tot eerdere publicaties, werden er geen verbeteringen in de lichaamslengte en botdichtheid tijdens etanercept behandeling gezien.

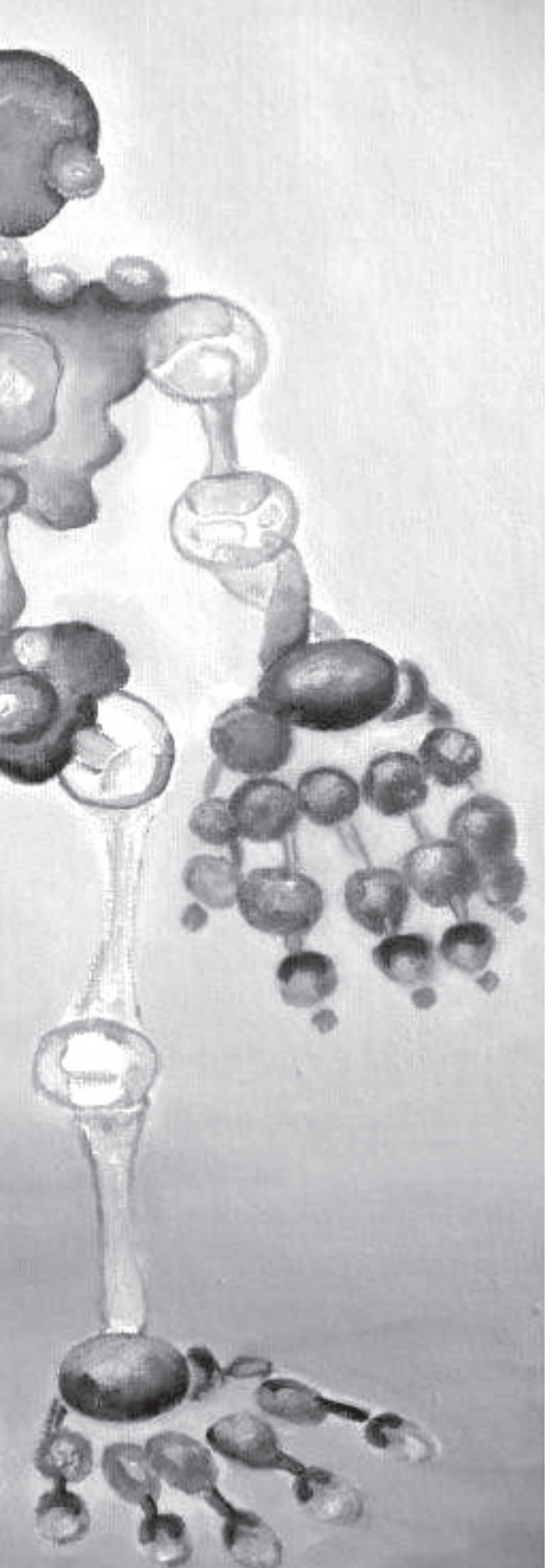
Verschillende behandelstrategieën na het falen van etanercept bij JIA werden beschreven in hoofdstuk 4. Hoofdstuk 4.1 illustreert een vertraagde klinische respons bij een aanzienlijk deel van de patiënten (55%) die eerder niet overtuigend reageerden na drie maanden behandeling met etanercept. Wij concludeerden dat, vooral bij patiënten met een gedeeltelijke primaire therapie respons, continuering van de behandeling voor

tenminste zes maanden moet worden aanbevolen. Hoofdstuk 4.2 rapporteert over het switchen tussen biologicals. Ongeveer 20% van de patiënten die werden behandeld met etanercept als eerste biological, kregen een tweede biological voorgeschreven. Na het onvoldoende responderen op etanercept, bleken zowel adalimumab als infliximab even effectief voor JIA patiënten met de niet-systemische JIA categorieën. Anakinra bleek superieur te zijn ten opzichte van een tweede TNF-alfa blokker voor patiënten met systemisch JIA. Over het geheel genomen was de effectiviteit van een tweede biological lager dan de eerste en leek deze vooral laag wanneer het eerste biological werd gestaakt als gevolg van primaire ineffectiviteit. We concludeerden dat het switchen tussen biologicals veilig lijkt te zijn en, omdat beperkte mogelijkheden beschikbaar zijn, te rechtvaardigen voor de JIA patiënten die niet respondeerden op etanercept.

Aangezien er in het Nederlandse ABC register meer dan 12 jaar aan observatie met behandeling van biologicals is vast gelegd en gedurende deze periode nieuwe middelen en nieuwe inzichten in de behandeling zijn opgedaan, zijn er verschillen in het voorschrijven van biologicals ontstaan en deze trends worden gepresenteerd in hoofdstuk 5. Hoofdstuk 5.1 beschrijft dat biologicals tegenwoordig steeds meer en eerder tijdens het ziektebeloop voorgeschreven worden. De ziekte activiteit van de JIA patiënten die in aanmerking kwamen voor een eerste biological daalde gedurende de jaren en deze daling in ziekte activiteit ging gepaard met betere korte termijn uitkomsten. Terwijl etanercept biological van eerste keuze voor JIA patiënten met niet-systemische JIA categorieën bleef, werd anakinra biological van eerste keuze voor systemische JIA patiënten. In hoofdstuk 5.2 worden de verschillen tussen de etanercept en adalimumab behandelde patiënt groepen gepresenteerd. Patiënten die behandeld werden met adalimumab werden gekenmerkt door de (vroegere) aanwezigheid van uveitis, door een langere duur van de ziekte en een lagere ziekte activiteit vergeleken met de etanercept behandelde patiënten. In een kwalitatieve focusgroep-analyse werd de aanwezigheid van uveïtis erkend door de geïnterviewde artsen als een van de belangrijkste factoren die hun keuze voor adalimumab beïnvloedde. Meer ervaring met en meer wetenschappelijke gegevens over etanercept en de pijnlijkheid van de adalimumab injecties waren de belangrijkste redenen om terughoudend te zijn met het voorschrijven van adalimumab.

In de bijlage (hoofdstuk 6) worden de resultaten van onze internationale samenwerking met Duitsland en Engeland naar laboratorium bepalingen bij systemische JIA patiënten, die behandeld worden met DMARDs en biologicals, gepresenteerd. Deze internationale onderzoeksgroep heeft de waarde van een specifieke biomarker ("toll-like receptor 4 agonist MRP8 en MRP14 eiwit complex") onderzocht en concludeerde dat deze biomarker sensitief voor de ziekte activiteit was en recidieven bij systemische JIA voorspelde.

Dit proefschrift wordt afgesloten met een algemene discussie beschreven in hoofdstuk 7. De verschillende lessen die uit dit proefschrift kunnen worden geleerd worden aangehaald en bediscussieerd in het licht van eerdere publicaties. Verder worden de methodologische overwegingen beschreven en de implicaties voor de dagelijkse klinische zorg en aanwijzingen voor toekomstig onderzoek besproken.



Appendices

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LIST OF FREQUENTLY USED ABBREVIATIONS

ABC	Arthritis and Biologics in Children, the Dutch national register
ACR	American College of Rheumatology
ACRpedi30	American College of Rheumatology paediatric 30, a measure of response
AE	adverse event
AS	ankylosing spondylitis
bDMARD	biologic disease modifying anti-rheumatic drug (also referred to as biologic or biologic agent)
BMAD	bone mineral apparent density (i.e. adjusted for volume)
BMD	bone mineral density
CHAQ	childhood health questionnaire
DMARD/ sDMARD	synthetic disease modifying anti-rheumatic drug
ERA	enthesitis related arthritis
ESR	erythrocyte sedimentation rate
IL	interleukin
ILAR	International League of Associations for Rheumatology
IQR	interquartile range
JIA	juvenile idiopathic arthritis
MRP	myeloid-related protein
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SEA	seronegative enthesopathy and arthropathy
SJIA	systemic juvenile idiopathic arthritis
TNF	tumour necrosis factor
VAS	visual analogue scale

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Marieke Henderika Otten was born in Leiden on December 28th, 1982. After graduating from high school in 2001 (Atheneum at the "Adelbert College" in Wassenaar), she studied Spanish in Spain and in Guatemala, worked as a volunteer at the Orphanage Casa Guatemala, Guatemala and travelled trough Central America.

In 2002 she moved to Maastricht and started her medical training at the University of Maastricht. She participated in both study and student related associations. In this period she became interested in paediatrics and she conducted a considerable part of her final year of medical training at the Erasmus MC Sophia Children's Hospital Rotterdam. There she participated in a research project on juvenile systemic lupus erythematosus at the department of paediatric rheumatology and improved her clinical skills during an internship at the out patient care and paediatric emergency department.

After obtaining her medical degree (in 2008) she worked for 7 months as a resident paediatrics (ANIOS) at the medium care and paediatric emergency department of the Erasmus MC Sophia Children's Hospital in Rotterdam (A.J. van der Heijden, M. de Hoog). Between November and December 2008 and since July 2009 she enrolled in the Arthritis and Biologics in Children research project, a collaboration between all Dutch university hospitals and hospitals with a special interest in paediatric rheumatology in the Netherlands and the research group of J. Roth in Muenster, Germany. Her PhD focuses on the effectiveness and safety of biologic treatments in juvenile idiopathic arthritis (Co-promoter L.W.A. van Suijlekom-Smit, Promoter A.J. van der Heijden). During her PhD period she obtained her Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam (in 2011). Furthermore, she jointly developed the protocol of the study "Withdrawal of Etanercept after Successful Treatment of Juvenile Idiopathic Arthritis" (ABC-STOP trial), funded by the Dutch Arthritis Association (Reumafonds). She participated in the training for upcoming leaders in paediatrics (TULIPS) PhD curriculum programme and she volunteered during a weekend for children with arthritis and their families in Barretstown, Ireland.

In July 2012 she will start her paediatrics training at the "Gelre Ziekenhuis" in Apeldoorn (C.H. Schröder) and at the Wilhelmina Children's Hospital in Utrecht (E.E.S. Nieuwenhuis, J. Frenkel).

Marieke likes to travel, read, run and play tennis. She is engaged to Bart Jan Rodenberg, who is a project manager in logistics, and together they live in Amsterdam.

LIST OF PUBLICATIONS

1. Marieke H. Otten, Femke H.M. Prince, Lisette W.A. van Suijlekom-Smit. Author reply. JAMA. 2012 Mar 21;307(11):1140-1.
2. Dirk Holzinger, Michael Frosch, Astrid Kastrup, Marieke H. Otten, et al. The Toll-like receptor 4 agonist MRP8 and MRP14 protein complex is a sensitive indicator for disease activity and predicts relapses in Systemic-Onset Juvenile Idiopathic Arthritis. Ann Rheum Dis. 2012 Jan 20. [Epub ahead of print]
3. Marieke H. Otten, Femke H.M. Prince, W. Armbrust, et al. Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. JAMA. 2011 Dec 7;306(21):2340-7.
4. Marieke H. Otten, Femke H.M. Prince, Marinka Twilt, et al. TNF-alpha blocking agents for children with enthesitis related arthritis; data from the Dutch Arthritis and Biologics in Children Register between 1999 and 2010. J Rheumatol. 2011 Oct;38(10):2258-63.
5. Femke H.M. Prince, Marieke H. Otten, Lisette W.A. van Suijlekom-Smit. Diagnosis and management of Juvenile Idiopathic Arthritis. BMJ 2010; 341:c6434
6. Marieke H. Otten, Femke H.M. Prince, Rebecca ten Cate, et al. TNF-blocking agents in juvenile psoriatic arthritis: are they effective? Ann Rheum Dis. 2011 Feb;70(2):337-40.
7. Femke H.M. Prince, Anna K. Dorai Raj, Marieke H. Otten, et al. TNF-alpha inhibitors for juvenile idiopathic arthritis (Protocol). Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD008598. DOI: 10.1002/14651858. CD008598.
8. Marieke H. Otten, Karlien Cransberg, Marion A.J. van Rossum, et al. Disease Activity Pattern in Juvenile Systemic Lupus Erythematosus and it's relation to Early Aggressive Treatment. Lupus 2010 Nov;19(13):1550-6
9. Marieke H. Otten, Femke H.M. Prince, Marinka Twilt, et al. Delayed Clinical Response in Patients with Juvenile Idiopathic Arthritis treated with Etanercept. J Rheumatology 2010;37:665-7
10. LN Moorthy, MGE Peterson, MJ Baratelli, AL Hassett, TJA Lehman and the International SMILEY Collaborative Group (Marieke H. Otten, member). Preliminary cross-cultural adaptation of a new pediatric health-related quality of life scale in children with systemic lupus erythematosus: an international effort. Lupus 2010 Jan;19(1):83-8

DANKWOORD

Tijdens de afgelopen 3 jaar heb ik ontzettend veel geleerd, zo nu en dan wat frustraties gekend, maar vooral enorm genoten. Een gek idee dat het nu echt klaar is. Aan de andere kant is dit pas het begin en ik hoop bij wetenschappelijk onderzoek betrokken te blijven. Onderzoek doe je nooit alleen en daarom wil ik graag in dit meest gelezen hoofdstuk van mijn proefschrift een aantal mensen bedanken.

Ten eerste wil ik alle betrokkenen binnen de ABC werkgroep bedanken voor hun inzet. Zonder de inspanning van deze (kinder)reumatologen uit het hele land en van alle betrokken reumaverpleegkundigen, fysiotherapeuten en doktersassistentes was het onmogelijk om alle data te verzamelen. Bedankt!

Maar zonder degene die dit alles leidde was dit proefschrift er niet gekomen. Lieve Lisette, zonder jouw begeleiding stond ik hier nu niet. Als student uit Maastricht ben ik bij jou begonnen met wetenschappelijk onderzoek. Eerst de kinderen met SLE "even" in kaart brengen. Een enorme klus, en zonder jouw doorzettingsvermogen was er geen publicatie uit voortgekomen. Toen jij mij vroeg Femke op te volgen heb ik geen seconde getwijfeld. Jouw betrokkenheid en oplossingsgerichtheid hebben tot mooie publicaties geleid. "Hoog" inzetten is jouw motto en daar had ik niet altijd vertrouwen in. Gelukkig hield je vol, wat uiteindelijk tot een top publicatie van het kroonstuk van dit proefschrift heeft geleid. Bedankt voor al jouw werk gerelateerde en persoonlijke adviezen, je bent de afgelopen jaren een echte mentor voor mij geweest. Wij genieten beiden van lekker eten en goede wijnen en ik hoop dat we de heerlijke diners zullen blijven voortzetten!

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Als laatste wil ik natuurlijk Bart bedanken. Er is niemand die mij zo goed kent als jij. Bedankt voor al je geduld, steun, liefde en kritische beoordeling van het Engels van mijn artikelen. Ik kan me geen leven voorstellen zonder jou. Ik houd van jou.

PHD PORTFOLIO: SUMMARY OF PHD TRAINING AND TEACHING

Erasmus MC Department: Paediatrics - Paediatric Rheumatology
Research School: NIHES
PhD period: Nov - Dec 2008 and Aug 2009 - June 2011
Promoter: Prof. Dr. A.J. van der Heijden
Co-promoter: Dr. L.W.A. van Suijlekom-Smit

1. PHD TRAINING

	Year	Workload (ECTS)
General academic skills		
Biomedical English Writing and Communication	2010	4.0
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1.0
Course Research Integrity	2012	2.0
PhD Curriculum TULIPS	2011-2012	4.0
Research skills		
Master of Science Clinical Epidemiology	2009-2011	40.0
Core curriculum		
Study Design	2009	4.3
Classical Methods for Data-analysis	2009	5.7
Clinical Epidemiology	2009	5.7
Methodological Topics in Epidemiologic Research	2010	1.4
Modern Statistical Methods	2010	4.3
In-depth courses		
Repeated Measurements in Clinical Studies	2011	0.9
Missing Values in Clinical Research	2011	0.7
Advanced Topics in Clinical Trials	2011	1.4
Advanced Analysis of Prognosis Studies	2011	0.7

	Year	Workload (ECTS)
Summer programme		
Principles of Research in Medicine	2009	0.7
Methods of Clinical Research	2009	0.7
Introduction to Decision-making in Medicine	2009	0.7
Clinical Decision Analysis	2009	0.7
Clinical Trials	2009	0.7
Pharmaco-epidemiology	2009	0.7
Conceptual Foundation of Epidemiologic Study Design	2010	0.7
Case-control studies	2010	0.7
Markers and Prognostic Research	2010	0.7
Health Economics	2010	0.7
Introduction to Public Health	2010	0.7
Primary and Secondary Prevention Research	2010	0.7
Advances in Epidemiologic Study Design	2010	0.4
Postgrade course "Write an article"	2008	0.5
The Nottingham Systematic Review Course (Cochrane)	2010	1.2
ACR Clinical research course Comparative Effectiveness Research, Chicago	2011	0.2
(Inter)national conferences		
Combined European Congress of Rheumatology (EULAR) and 16th Pediatric Rheumatology European Society Congress, Copenhagen [1 oral and 2 poster presentations]	2009	1.4
Young Investigators Meeting 16th Pediatric Rheumatology European Society Congress Copenhagen [1 oral and 1 poster presentation]	2009	0.5
European Congress of Rheumatology (EULAR), Rome [2 poster presentations]	2010	1.0
17th Pediatric Rheumatology European Society Congress, Valencia [2 poster presentations]	2010	1.0
Young Investigators Meeting 17th Pediatric Rheumatology European Society Congress, Valencia [2 poster presentations]	2010	0.5

	Year	Workload (ECTS)
18th Pediatric Rheumatology European Society Congress, Brugge [oral presentation]	2011	1.4
Young Investigators Meeting 18th Pediatric Rheumatology European Society Congress, Brugge	2011	0.5
American College of Rheumatology meeting Chicago [2 poster presentations]	2011	1.0
Combined European Congress of Rheumatology (EULAR) and 19th Pediatric Rheumatology European Society Congress, Berlin [1 poster presentation]	2012	1.0
Seminars and workshops		
PhD-day, Sophia Children's Hospital Rotterdam	2008-2010	0.9
Young Investigators Day, Paediatric Association of the Netherlands	2009-2011	0.9
Investigators Meeting, The Cherish Study, Paris	2009	0.5
Symposium 'Biologics en kinderen: een update'	2010	0.3
Symposium 'Een caleidoscoop van de kinderreumatologie' [oral presentation]	2011	1.0
2. TEACHING		
Supervising Master's theses		
A. Thio, student Medicine, Erasmus MC. Thesis title: Bone density status in Juvenile Idiopathic Arthritis patients treated with etanercept	2010	3.0
Other		
Peer review of articles for international scientific journals	2010-2012	3.0