Etanercept in Juvenile Idiopathic Arthritis: Results from the Dutch National ABC register Femke H.M. Prince

Ballet is all about balance. This requires great physical strength from the performer, especially from the joints and muscles. For children with Juvenile Idiopathic Arthritis (JIA) balance is a problem, since the disease causes pain and disability in the joints. JIA itself is caused by an imbalance in the immune system. Etanercept therapy aims to restore this balance. This thesis describes long-term effectiveness and safety, as well as the balance in dose, continuation and discontinuation, of etanercept in JIA.

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resultaten uit het Nederlandse nationale ABC register

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Een schip dat naar de horizon vaart
verdwijnt niet

Voor mijn lieve broer Joep

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Part 1

Introduction

Chapter 1

General introduction

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile Idiopathic Arthritis (JIA) is the most common cause of chronic arthritis in childhood, one in 1000 children worldwide is effected.[1-3] It is characterized by joint inflammation leading to joint destruction and frequently results in physical disabilities and chronic pain influencing daily life.[4,5] JIA is a heterogeneous disease comprising several disease subtypes. Chronic childhood arthritis was already extensively described by George Frederic Still in 1896 and although the exact etiology remains unknown, much progress in the understanding of the disease has been made.[2,6,7] The term encompasses all forms of arthritis that begin before the age of 16 years and persist for more than 6 weeks.[2,7] Other known causes should be excluded (table 1.1). Gender ratio is different per JIA subtype, but in general there are more females than males affected. More than 50% of children with JIA enter adulthood with ongoing active disease.[8]

Terminology has changed during the last years. Since 1977 in Europe the classification consistent with the term Juvenile Chronic Arthritis (JCA) was used and in North America paediatric rheumatologists adhered to the terminology and classification of Juvenile Rheumatoid Arthritis (JRA).[10,11] In an effort to come to a universally accepted system of classification the umbrella term Juvenile Idiopathic Arthritis was introduced by the International League of Associations of Rheumatologists.[12] The new classification system was revised twice and is now worldwide accepted (table 1.2).[7,13]

Complications of JIA may vary from local to systemic depending on the subtype and severity of the disease and treatment given.[9] Long-term localized joint inflammation may lead to flexion deformities, damage of cartilage and bone. Bony overgrowth may cause length discrepancies. Also disturbance of overall growth is a problem in JIA, and is due to the disease itself but also other factors such as use of glucocorticoids.[15,16] Anemia is recognized as a result of the chronic disease process. Systemic JIA (sJIA) is associated with the most serious morbidity.[17] Conditions associated with this subtype include amyloidosis and macrophage activation syndrome (MAS).[18,19]

Table 1.1: Differential diagnosis of joint complaints in children[9]

1. Arthritis
Infective and reactive; Lyme disease, viral infection, mycoplasma, poststreptococcen
Juvenile idiopathic arthritis
Connective tissues disorders: SLE, dermatomyositis, systemic sclerosis
Systemic vasculitis; Henoch-Schonlein purpura, Kawasaki, Polyarteritis nodosa
Other: haemophilia; immune deficiency (including periodic fever syndromes); sarcoidosis
2. Mechanical/ degenerative
Trauma: accidental and non-accidental
Hypermobility
Avascular necrosis including Perthes, Osgood Schlatters, Scheuermanns
Slipped upper femoral epiphyses
Anterior knee pain including chondromalacia patallae
3. Non-organic
Idiopathic pain syndromes: diffuse or localised (reflex sympathetic dystrophy)
Benign nocturnal idiopathic limb pains (growing pains)
Psychogenic
4. Other
Osteomyelitis
Tumours; malignant (leukaemia, neuroblastoma) or benign (osteoid osteoma, pigment villonodular synovitis)
Metabolic abnormalities; rickets, diabetes, hypophosphataemic rickets, hypo/ hyperthyroidism
Genetic disorders; skeletal dysplasias, mucopolysccharidoses, collagen disorders (Ehler's Danlos, Stickler syndrome)

Table 1.2: Characteristics of the JIA subtypes[2,7,14]

JIA subtype	Percentage of total JIA patients	Onset age	Sex ratio F : M
Systemic JIA (sJIA)	4-17	Throughout childhood	1 : 1
Oligoarticular	27-60	Early childhood (peak 2-4 years)	5 : 1
Persistent (oJIA pers)	40		
Extended (oJIA ext)	20		
Polyarticular Rheumatoid Factor positive (pJIA RF+)	2-7	Late childhood or adolescence	3 : 1
Polyarticular Rheumatoid Factor negative (pJIA RF-)	11-30	Early peak 2-4 years and late peak 6-12 years	3 : 1
Psoriatic arthritis (PsJIA)	2-11	Late childhood or adolescence	1 : 0.95
Enthesitis-related arthritis (ERA)	1-11	Early peak 2-4 years and late peak 9-11 years	1 : 7
Undifferentiated arthritis (uJIA)	11-21		

TREATMENT OF JIA

Since there is currently no cure for JIA, the goal of treatment is disease remission. The management of JIA has in the past relied on nonsteroidal anti-inflammatory drugs (NSAIDs) with slow addition of synthetic disease modifying anti-rheumatic drugs (DMARDs) and thereafter biologic DMARDs (biologicals), with avoidance of systemic glucocorticoids.[3] However, evidence is accumulating that early disease control is important to prevent joint destruction, growth deformities and even blindness (from chronic uveitis associated with JIA). Therefore, trials are performed in JIA patients to investigate the importance of early aggressive treatment.[3,20]

NSAIDs

NSAIDs inhibit the cyclooxygenase pathway of arachidonate metabolism, preventing formatation of the proinflammatory prostaglandines.[21] In oligoarticular JIA (oJIA) NSAIDs are often used as monotherapy, however in polyarticular course JIA effectiveness is low and side effects are frequent.[22]

Glucocorticoids

Glucocorticoids (steroids) are used selectively in JIA.[9] Intraarticular (IA) glucocorticoids are increasingly used and are safe and effective, especially in oJIA persistent.[23,24] Systemic steroids are useful for short-term administration to induce inactive disease and in bridging when during inactive disease short periods of disease flare occur, but are preferably not used on the long-term due to unacceptable side effects. Unfortunately, a substantial part of the sJIA patients rely on systemic glucocorticoids to control disease activity.[25]

DMARDs (synthetic)

Methotrexate (MTX) has become the second-line drug of choice for JIA patients for whom NSAIDs and/ or IA glucocorticoids are ineffective or inappropriate.[21] It is a folic acid analog that binds more tightly to dihydrofolate reductase than does folic acid and causes reduction of the production of reduced folates, which are important cofactors for a variety of enzymatic pathways.[25] In low doses used in the treatment of JIA (0.3-1.0 mg/kg/week), MTX therapy also results in increased adenosine release at inflammation sites and the interference with the action of IL-1, production of IL-8 and leukotriene B4, and decreased synovial collagenase gene expression.[26] MTX is not only very effective in great part of the JIA patients, it is usually well tolerated and does not appear to be more toxic than NSAIDs if monitored properly.[25,27]

Sulfasalazine (SSZ) is able to improve arthritis in patients with oJIA, pJIA and enthesitis-related arthritis (ERA).[28-31] It has both anti-bacterial and anti-inflammatory effects. Side effects are generally mild.

Hydroxychloroquine, and azathioprine are also regular used in treating JIA patients but seem less effective compared to MTX and SSZ. Although Cyclosporin seems less effective for treating arthritis in JIA, it is successfully used intravenously for treating MAS associated with sJIA.[25]

Biologicals

Biologicals (biological DMARDs) are designed to target inflammatory cytokines. One of most prominent of these cytokines is Tumour Necrosis Factor (TNF) since it plays a central role in the pathogenesis of JIA.[32] In sJIA, also other cytokines such as Interleukin(IL)-1 and IL-6 are thought to be key cytokines.

Only etanercept, adalimumab and abatacept (latter only in USA) are approved for JIA, other biologicals are prescribed off-label.

TNF-alpha blocking agents

Etanercept is one of the TNF-alpha blocking agents and was the first biological registered for JIA in 1999. It binds to TNF-α and TNF-β (lymphotoxin-α) preventing it from interacting with the receptors on the cell surfaces. A controlled study in polyarticular course JIA patients, refractory to MTX therapy, has shown the efficacy, at a subcutaneous (SC) dose of 0.4 mg/kg twice weekly.[33]

Adalimumab is a monoclonal antibody to TNF and is given in 40mg SC every two weeks. Efficacy was proven in randomized, placebo-controlled, double-blind clinical trial.[34] Based on the results from this trial adalimumab was the second biological to be registered for JIA in 2008.

Infliximab is a chimeric human/ mouse anti-TNF monoclonal antibody, which binds to TNF-alpha preventing it to bind to cell-surface receptors. A randomized, placebo-controlled double-blind study showed no distinct efficacy of infliximab therapy in the dose of 3 mg/kg or 6 mg/kg intravenously, but authors argue that the dose of 3 mg/kg was too low and placebo response was higher than expected.[35] Infliximab is usually given in the dose of 6-10 mg/kg intravenously at 0, 2 and 6 weeks, followed by every 4-8 weeks thereafter, depending on severity of disease and response to therapy. MTX has to be given concomitantly to prevent the development of antibodies against infliximab.[25]

Adalimumab and infliximab appear to be more effective in treating JIA associated uveitis, compared to etanercept.[36-41]

T-cell co-stimulation modulator

Abatacept selectively inhibits T cell activation by binding to CD80/CD86. This in turn prevents the second co-stimulatory signal which helps in activating the inflammatory pathway.[42] Efficacy and general tolerability of abatacept in JIA patients was shown in a double-blind, randomized controlled withdrawal trial. The United States FDA approved abatacept for the treatment of JIA patients who have had an inadequate response to one or more DMARDs such as MTX or TNF antagonists. Abatacept is administered by intravenous infusion at 10 mg/kg at day 0, 2 weeks, 4 weeks, and every 4 weeks thereafter.

IL-1 receptor antagonists

IL-1 is a proinflammatory cytokine synthesized by macrophages (and fibroblasts in the synovium). Anakinra is a fully human recombinant IL-1 receptor antagonist (RA) and is most useful in sJIA. Efficacy and short-term safety of anakinra, given 1mg/kg/day SC, was shown in a randomized controlled study with JIA patients of different subtypes.[43]

IL-6 receptor antibody

IL-6 is the other proinflammatory that is elevated in sJIA patients. IL-6 levels correlate with fever, disease activity and platelet counts. Tocilizumab is an anti-IL-6-receptor monoclonal antibody.[44] A controlled study in sJIA patients showed efficacy and safety after 18 weeks of tocilizumab, given intravenously in the dose of 8 mg/kg every two weeks.

B-cell antagonists

Rituximab is only occasionally used in the treatment of JIA. It is a monoclonal antibody that binds to the CD20-antigen on B-lymphocytes with results in the depletion of B cells. This helps to reduce the amplification process in the inflammatory pathway.[45] Preliminary results suggest that rituximab seems to be a useful therapeutic alternative in patients with active sJIA in whom previous treatments (including TNF-alpha antagonists and anakinra) have failed.[46]

Stem cell transplantation

Autologous stem cell transplantation is used as treatment in autoimmune diseases and several JIA patients have been successfully transplanted.[47] However, since there are great risks involved in this procedure (transplant-related mortality rate 9%), this therapy should be reserved for JIA patients who remain resistant to combinations of synthetic DMARDs, corticosteroids and biologicals and suffer from a very severe, debilitating and potentially fatal disease.[48]

Non-drug management

Also non-drug therapy is an important aspect of the management of JIA. Physiotherapy is important to maintain normal muscle and joint function. Rehabilitation therapy is crucial to be able to carry out activities of daily living. Also, psychological therapy and education about the disease are important support for the patient and the family.[2,9]

OUTCOME ASSESSMENT IN JIA

Clinimetrics is a methodologic discipline that focuses on the quality of clinical measurements of, for example, disease outcomes. Different clinimetric properties, such as reproducibility and responsiveness, are important in both the development and the evaluation of measurement instruments.[49] Several measurement instruments to evaluated disease outcome were introduced within paediatric rheumatology and tested according to the clinimetric concepts. The ones that are now considered the golden standard to assess JIA disease outcome, are summarized.

ACR Pedi criteria

To standardize the assessment of clinical response of JIA patients in clinical trials, Giannini et al. identified a core set of outcome variables (table 1.3).[50]

Table 1.3: Response variables of the JIA core set[50]

1. overall assessment of the disease activity by the physician through the visual analogue scale (VAS) (range 0-100 mm, 0 best score)
2. childhood health assessment questionnaire (CHAQ) (range 0-3, 0 best score) by the patient or parent
3. overall assessment of well-being by the patient or parent through the VAS (range 0-100 mm, 0 best score)
4. number of active joints (joints with swelling not caused by deformity, or joints with limited motion, and with pain, tenderness, or both)
5. number of joints with limited motion
6. a laboratory marker of inflammation; erythrocyte sedimentation rate (ESR)

Subsequently, they developed a definition of improvement to determine whether individual patients demonstrate clinically important improvements. These criteria are commonly known as the American College of Rheumatology Pediatric criteria (ACR Pedi). The ACR Pedi 30 states that there should at least be a 30% improvement from baseline in 3 of any 6 variables in the JIA core set, with no more than one of the remaining variables worsening by more than 30%.

The ACR Pedi criteria are now also used in other types of study and improvement guidelines were expanded with the ACR Pedi 50, 70, 90 and 100 indicating an improvement from baseline of at least 50%, 70%, 90% or 100% respectively in 3 of any 6 variables in the JIA core set, with no more than 1 of the remaining variables worsening by more than 30%.[51]

Inactive disease and clinical remission

To evaluate the disease status criteria for inactive disease and clinical remission were proposed by Wallace et al.

Criteria for inactive disease, either on medication (IDM) or off medication (ID), were defined as: no active arthritis, no fever, rash, serositis or generalized lymphadenopathy attributable to JIA, no active uveitis, normal ESR and a physician's overall assessment of disease activity that indicated no disease activity.[52,53]

In case of clinical remission on medication (CRM), criteria of IDM had to be met for more than six months. In case of clinical remission off medication (CR), criteria for ID had to be met for more than twelve months.[52,53]

Although the remission criteria by Wallace et al. were not specifically developed for the JIA subtypes Juvenile Arthritis Psoriatica (PsJIA) or Enthesitis Related Arthritis (ERA), these criteria are used to evaluated disease activity in patients with these subtypes since no other remission criteria are currently available. In addition, it can be noted if psoriatic lesions or active entheses were presented.

ARTHRITIS AND BIOLOGICALS IN CHILDREN (ABC) PROJECT

In 1999 TNF-alpha blocking agents were introduced as a new therapeutic option in the treatment of Juvenile Idiopathic Arthritis (JIA). In the Netherlands, patients with a polyarticular course and insufficient response to a maximum (tolerated) dose methotrexate are eligible for treatment with TNF-alpha blocking medication.

In 2000 a central evaluation board has been installed at the moment TNF-alpha blocking medication was included in the Medications Reimbursement System (GVS) by the Ministry of Health, Welfare and Sport. This central evaluation board had to give approval for reimbursement of TNF-alpha blocking agents for each JIA patient (according to the requirements listed above) before start of treatment. They also evaluated the clinical

improvement of each patient after three months of treatment and decided on continuation of reimbursement accordingly. However, exceptions were made in case of supportive arguments from the treating physician, such as reducing concomitant drugs during etanercept therapy.

Secondly, the Ministry of Health, Welfare and Sport conditioned a study on efficacy and cost-effectiveness in JIA financed by the Dutch Board of Health Insurances (CVZ) from 2003-2006. All patients treated with TNF-alpha blocking medication since 1999 were included in this Dutch national survey.[54] In 2007 we initiated a web-based national register for JIA patients, treated with all different kinds of biologicals, in the Netherlands. This web-based register was launched in 2008 as a collaboration of all paediatric rheumatology centres in the Netherlands.[55] All patients from the initial study and all other JIA patients that started treatment with a TNF-alpha blocking agent or other biological are included in the register. Today (September 2009) more than 300 patients are included, most frequently treated with etanercept due to the fact that this was until recently the only registered biological for JIA.

Data collected in the register at baseline are; patient and disease characteristics including date of birth, gender, date of JIA onset, JIA subtype, extra-articular manifestations (including uveitis) and detailed information on previous medication. The disease activity is evaluated by means of the JIA core set of response variables. Also, a radiological and bone density evaluation is conducted and sera samples are collected.

Patients are re-evaluated at fixed time-points (3, 6, 15 months and every year thereafter) by means of the JIA core set of response variables. At the same time data on existence of extra-articular manifestations and sera samples are collected. Improvement in disease activity is determined using the criteria of improvement according to the ACR Paediatric by Giannini et al. and the criteria of inactive disease and clinical remission by Wallace et al.[50,56] Detailed information on the treatment with all biologicals used (dose, changes and reasons) and concomitant medication is obtained and adverse events are monitored. The radiological and bone density evaluation is repeated every year.

With the automatically generated SPSS-database from the ABC-register different research questions can be answered.

AIM AND OUTLINE THESIS

The main objective of the research described in this thesis was to evaluate the long-term effectiveness and safety of etanercept in JIA, in all different subtypes, in a real-life setting. Studies were conducted to answer the following research questions:

1. What is the long-term effectiveness of etanercept to control disease activity in JIA?
2. What is the long-term safety profile of etanercept in JIA?
3. What is the effect of etanercept on the health-related quality of life in JIA?
4. What is the cost-effectiveness of etanercept in JIA?
5. What is the optimal use of etanercept in JIA?

Chapter 2 gives an overview of the current literature on etanercept in JIA. Chapter 3 and 4 cover the methodology of data collection in the ABC-register and systematic evaluation of disease activity in daily practice. In chapter 5, 6 and 7 the long-term effectiveness and safety of etanercept in JIA are evaluated. Effectiveness is described as the ability of etanercept to reduce disease activity, improve health-related quality of life and reduce costs in health care. Several studies on the evaluation of treatment strategies are discussed in chapter 8, 9 and 10. The general discussion in chapter 11 answers the main research questions of this thesis, as described in chapter 1. Finally, in chapter 12 a summary of this thesis is given.

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Chapter 2

Review of the literature on etanercept in Juvenile Idiopathic Arthritis

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Submitted for publication under the title

A decade of etanercept therapy in Juvenile Idiopathic Arthritis; what have we learned so far?

INTRODUCTION

Juvenile Idiopathic Arthritis

Juvenile Idiopathic Arthritis (JIA), formerly known as Juvenile Rheumatoid Arthritis (JRA) or Juvenile Chronic Arthritis (JCA), is the most common cause of chronic arthritis in childhood, approximately one in 1000 children worldwide is effected.[1-3] It is characterized by joint inflammation leading to joint destruction and frequently results in physical disabilities and chronic pain influencing daily life.[4,5] JIA is a heterogeneous disease; the term encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown cause.[1,2] The different JIA subtypes are described in table 2.1. Gender ratio is different per JIA subtype, but in general more females than males are affected. More than 50% of children with JIA enter adulthood with ongoing active disease.[6,7]

Although management and treatment response differ between subtypes, in recent years the therapy strategies have changed from a slow add-on approach in favor of the early introduction of DMARDs, occasionally in combination with steroids, with aggressive addition of further agents (such as etanercept) with a target of disease remission. This new treatment strategy is very successful in suppressing disease activity, slowing progression of joint destruction, and improving long-term outcome in a great part of the JIA patients. Since its introduction in 1999 etanercept has become an important treatment option for patients with Juvenile Idiopathic Arthritis (JIA), who previously did not respond to synthetic DMARDS including methotrexate (MTX).[7-13]

Table 2.1: Classification JIA subtypes according to ILAR[1]

Classification		
Categories	**Criteria**	**Exclusions**
Systemic JIA (sJIA)	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis	1 to 4
Oligoarthritis	Arthritis affecting one to 4 joints during the first 6 months of disease	1 to 5
Persistent (oJIA pers)	Affecting not more than 4 joints throughout the disease course	
Extended (oJIA ext)	Affecting a total of more than 4 joints after the first 6 months of disease	
Polyarthritis Rheumatoid Factor positive (pJIA RF+)	Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive	1, 2, 3, 5
Polyarthritis Rheumatoid Factor negative (pJIA RF-)	Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative	1 to 5
Psoriatic arthritis (PsJIA)	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative	2 to 5
Enthesitis-related arthritis (ERA)	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative	1,4,5
Undifferentiated arthritis (uJIA)	Arthritis that fulfils criteria in no category or in 2 or more of the above categories	
Exclusions		
	1. Psoriasis or a history of psoriasis in the patient or first-degree relative	
	2. Arthritis in an HLA-B27 positive male beginning after the 6th birthday	
	3. Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative	
	4. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.	
	5. The presence of systemic JIA in the patient	

Etanercept

Etanercept, a TNF (tumor necrosis factor) inactivating biological agent, is a soluble, dimeric fusion protein consisting of two copies of the extracellular ligand-binding protein of the human p75 TNF receptor linked to the constant protein of the immunoglobin G1.[14] It binds to Tumor Necrosis Factor (TNF)-α and TNF-β (lymphotoxin-α) preventing it from interacting with the receptors on the cell surfaces.[15,16] TNF is a proinflammatory cytokine that plays an important role in de cascade of inflammatory processes in JIA. It is elevated in both the serum and the synovial fluid and the level is correlated with disease activity.[17,18]

Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons and is part of the class of drugs called biologicals.[19] Biologicals have been developed to have biologic properties and include monoclonal antibodies, soluble cytokine receptors and recombinant antagonist.[20]

JIA patients with polyarthritis are usually first treated with synthetic DMARDs, most commonly MTX (0.2-1.0 mg/kg/week), often in combination with Non-Steroid Anti-Inflammatory Drugs (NSAIDs), and sometimes complemented with local or systemic glucocorticoids.[21,22] However, the use of glucocorticoids, especially systemic, is not recommended for long-term use due to their adverse effects, particularly on growth. The change of success of MTX therapy is largely influenced by the JIA subtype, sJIA patients respond most poorly and oJIA ext patients respond the best.[23-25] In most countries, etanercept is licensed and recommended for children with polyarticular course JIA after failure or intolerance to the maximum dose MTX.[22,26,27] About three quarters of JIA patients who start etanercept therapy, use MTX as concomitant drug.[26,27]

Evaluating the effect of etanercept

An increasing number of studies use the JIA core set of response variables designed by the American College of Rheumatology (ACR) to measure the effect of a treatment, including an improvement definition according to the ACR Pediatric 30, 50 and 70 criteria (ACR Pedi 30, 50 and 70).[19] This definition states that there should be at least 30% improvement (50% or 70% dependent on the score) from baseline in three of any six variables in the core set with no more than one of the remaining variables worsening by > 30%.

The core set exists of the following set of six response variables:

1. overall assessment of the disease activity by the physician through the visual analogue scale (VAS) (range 0-100 mm, 0 being best possible score);
2. childhood health assessment questionnaire (CHAQ) (range 0-3, 0 being best possible score) by the patient or parent;
3. overall assessment of well-being by the patient or parent through the VAS (range 0-100 mm, 0 being best possible score);
4. number of active joints (joints with swelling not caused by deformity, or joints with limited motion, and with pain, tenderness, or both);
5. number of joints with limited motion;
6. a laboratory marker of inflammation; erythrocyte sedimentation rate (ESR) or (CRP).

Also, criteria are used to indicate an inactive disease state or remission as defined by Wallace et al.[28,29] Criteria for inactive disease, either on medication (IDM) or off medication (ID), are defined as: no active arthritis, no fever, rash, serositis or generalized lymphadenopathy attributable to JIA, no active uveitis, normal ESR and a physician's overall assessment of disease activity that indicated no disease activity.[28,29] In case of clinical remission on medication (CRM) criteria of IDM had to be met for more than six months. In case of clinical remission off medication (CR) criteria for ID had to be met for more than twelve months. Although the remission criteria by Wallace et al. were not specifically developed for the JIA subtypes PsJIA or ERA, these are used since no other remission criteria are currently available. In addition, it should be mentioned if psoriatic lesions or active entheses were presented.

Aim of the review

The aim is to give a complete overview of the clinical information on the use of etanercept in patients with JIA.

METHODS

Search strategy

We searched on MEDLINE (1990-August 2009) and EMBASE (1990-August 2009). MeSH terms used were 'etanercept' and 'Juvenile Idiopathic Arthritis', 'Juvenile Rheumatoid

Arthritis' and 'Juvenile Chronic Arthritis'. We also searched for 'Enbrel' and 'juvenile arthritis' as text words. We included only articles written in English. We did not limit our searches to only paediatric populations, however we did require the papers to describe the patients with JIA, JRA or JCA separately. There was no restriction on the type of study described. We excluded duplicate reports, and took into account that some articles described (part of) the same patient group.

Outcomes measures

We extracted data from the papers on efficacy, effectiveness, safety and use.

If supplied by the authors the American College of Rheumatology Pediatric 30, 50 and 70 criteria (ACR Pedi 30, 50 and 70) were used to describe effectiveness.[19]

RESULTS

Pharmacokinetics and pharmacodynamics

Etanercept is slowly absorbed after subcutaneous (SC) injection. In adults it reaches its peak about 50 hours after injection and is cleared from the body with a reported half-life of 115 hours.[30] In JIA patients the mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Limited data suggests that the clearance of etanercept is reduced slightly in children ages 4 to 8 years (< 23kg).[31]

Initially the recommended dosing regimen for etanercept in JIA patients was 0.4 mg/ kg (maximum 25 mg) twice weekly SC.[13] However, studies in Rheumatoid Arthritis and Ankylosing Spondylitis show that the administering of an once weekly double dose is effective enough to induce and retain remission.[32,33] A pharmacokinetic model developed by Yim et al. shows that the computer simulated concentrations of etanercept in children of 0.8 mg/ kg SC once weekly dosing has widely overlapping concentration profiles with the usual dosing regimen of 0.4 mg/kg SC twice weekly at steady state.[31] Two clinical studies confirm the effectiveness and safety of the once weekly dose. The study from The Netherlands shows 11 patients retaining remission after a switch from the twice to the once weekly dose and 6 patients initiated on an once weekly dose of 0.8 mg/ kg who all show an improvement of at least the ACR Pedi 50 score after 12 weeks.[34,35] The German study described 20 patients in whom etanercept was initiated in 0.8 mg/ kg once weekly and a ACR Pedi 30, 50 and 70

was reached in respectively 95%, 75% and 75% after 12 weeks.[36] Also described, were six JIA patients who were switched to the once weekly dose; treatment was effective and well-tolerated.(37) In both studies there were no reports of SAEs.[34-37]

Although the recommended maximum dose etanercept for children is 50 mg per week (same as adults), one study demonstrates that it is safe to administer the higher dose of 0.8 mg/kg SC twice weekly to children (maximum dose 100 mg per week).[38] No studies until now have shown a good additional improvement due to raise in usual dose.[38,39]

Efficacy and effectiveness

Disease activity

We found 26 published manuscripts which evaluated the effect of etanercept on disease activity.[13,21,26,27,38-59] These included one publication on a randomized controlled study followed by 3 reports on the open label extension of this study, 11 reports on open prospective observational studies, 8 case reports or case series, 2 retrospective chart reviews, and one report on a survey. Studies with more than 5 patients included are summarized in table 2.2.

The efficacy and safety of etanercept in JIA was first assessed in a double-blind, randomized controlled withdrawal trial by Lovell et al.[13] Efficacy was expressed in percentage of patients with improvement according to the American College of Rheumatology Pediatric (ACR Pedi) response criteria, however the variable "number of limited joints" was modified to exclude joints with contractures that might not have improved during the short course of the study.[19] The study was conducted in two fases in 69 children with active polyarticular-course JIA. Subtypes included were sJIA, pJIA and oJIA ext. Patients ages 4 to 17 years with JIA, refractory to or intolerant of MTX were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). First, all patients received 0.4 mg/kg (maximum 25 mg per dose) etanercept SC twice weekly. In the second phase, patients with a clinical improvement according to the criteria of the ACR Pedi 30 at day 90 were randomized to remain on etanercept or receive placebo for four months and assessed for disease flare. Outcomes are shown in table 2.2 and figure 2.1. The majority of patients on placebo experienced a flare and etanercept was successfully reintroduced in these patients. All patients on etanercept at the end of the 7-month clinical trial were observed in a open label extension study.[48] Sustained effectiveness in these patients was shown after 2, 4 and 8 years of etanercept therapy (table 2.2 and figure 2.1).[48-50] Of the 69 patients, 26 entered the eighth year of treatment with etanercept. It should

be taken into account that of the 69 patients originally enrolled in the randomized, controlled study, 58 patients, in whom etanercept therapy was proved to be effective, were enrolled into the open-label extension study. Further analyses were based on a last-observation-carried-forward analysis in these 58 patients.

Next to this controlled study preformed prior to registration, other studies have reported on the effectiveness and safety of etanercept in JIA (table 2.2). In 2003 Quartier et al. reported effectiveness of etanercept according to the JIA subtype and showed a higher rate of treatment failure in the sJIA patients.[21] Subsequently, in the intention-to-treat analysis the initial improvement in the ACR Pedi 30 in 73% of the patients decreased to 39% after 12 months.

Horneff et al. first reported on a long-term registry in 2004. In this German register (with also some patients from Austria) they had included a total of 322 JIA patients and results from these patients showed that etanercept can be very effective already after one month in the majority of the patients (table 2.2 and figure 2.1). Sustained improvement was shown up to 48 months. A publication from the Dutch national register, named the Arthritis and Biologicals in Children (ABC) project, reported 146 JIA patients on etanercept. Again rapid improvements were seen and sustained up to 75 months. This study also showed that in the long-term an equal number of sJIA patients reached disease remission compared to other subtypes. This finding was supported by results from the German register in 2009, which showed that the sJIA patients who continued etanercept for 24 months had an equal improvement of their disease activity as patients with other subtypes.[60]

All these studies confirm that the effectiveness of etanercept extends beyond trial conditions to everyday clinical practice. An overview of the effectiveness of etanercept per JIA subtype is given in table 2.3.

It has been suggested that starting etanercept earlier in the disease course would be beneficial for especially sJIA patients.[21,61] However, a study in sJIA patients in the USA did not find statistic significantly differences in disease duration between responders and non-responders.[45] Currently, in the USA a trial is being conducted on early aggressive drug therapy (including etanercept) in JIA.[62]

Concomitant medication

All studies, except the initial randomized, controlled trial prior to registration of etanercept, allow patients to use concomitant medication, as prescribed by their physician, while treated with etanercept. Horneff et al. compared the safety and effectiveness of JIA patients in the

German registry who use etanercept in combination with MTX compared to patients with etanercept only.[26] Both groups (100 patients on monotherapy and 504 on combination therapy) showed good long-term effectiveness and tolerability was comparable. However, the groups differed significantly in several baseline variables such as JIA subtype and severity of disease activity, which makes an objective comparison difficult, since bias by indication played a role. Giannini et al. compared patients who received MTX alone (n = 197), with patients who received etanercept in combination with (n = 294) and without MTX (n = 103).[59] They concluded that both treatments with etanercept alone as etanercept plus MTX have an acceptable safety and effectiveness profile in patients with sJIA, pJIA RF+, pJIA RF- and oJIA ext.

Being able to reduce a great portion of concomitant medication is a major advance in the treatment of JIA. Most studies on effectiveness of etanercept in JIA report that a great part of the patients were able to discontinue or lower the dose of concomitant medication.[26,27,38,39,41-43,45,46,52,55,57,58] Especially systemic glucocorticoids could be completely discontinued in about two third of the patients using it at start of treatment. MTX use was lowered or discontinued in approximately a quarter of the patients using it as concomitant drug at start of etanercept. If etanercept was not effective enough or if a disease flare occurred MTX or systemic glucocorticoids were reintroduced in most cases. In all most all cases other DMARDs were discontinued during treatment with etanercept.

Radiographic improvements and bone density

Juvenile idiopathic arthritis (JIA) has been associated with both local and generalized growth retardation and osteopenia or osteoporosis.[66-68] It affects even patients not treated with glucocorticoids.[69,70] The influence of proinflammatory cytokines such as TNF-α in synergy with interleukin 1-β on the production of insulin-like growth factors (IGFs) has been presumed. In addition to improving clinical outcomes, etanercept prevents further radiographic progression and restores normal growth by rapid suppression of inflammation and specific interaction with bone metabolism.[66,67]

In an Italian study 40 JIA patients showed a reduced progression of radiological damage measured by the Poznanski score (carpo-metacarpal ratio) after one year of treatment with etanercept.[71]

Table 2.2: Studies on effectiveness of etanercept in JIA with more than 5 patients

Year	Author	Ref no.	Study design	Country	No. of patients	Follow-up time in years (median)	No. of patients-years	Disease duration at start (years)
2000	Lovell	13	3 mo open label, followed by 4 mo double-blind RCT	USA	69	0.6 (0.6)	40.3*	mean 5.9
2001/ 2002	Kietz	57, 58	open prospective observational	USA	22	2 (1.8)	30.8*	median 3.7
2001	Schmeling	53	case serie	Germany	7	0.5 (0.5)	3*	mean 4.6/ median 4.0
2001	Takei#	38	retrospective chart review	USA	8	1 (?)	10.1	mean 5.3/ median 4.8
2002	Cairns	40	open prospective observational	Northern Ireland	6	2 (?)	12*	?
2002	Haapasaari	41	retrospective chart review	Finland	31	1 (?)	28.8*	mean 6.3
2002/ 2009	Russo	39, 52	open prospective observational	Argentina	45	3.5 (2.0)	121.2	median 3
2003/ 2006/ 2008	Lovell	48-50	open label extension	USA	43/ 34/ 26	8 (?)	107/ 225/ 318	mean 5.9/ median 5.5
2003	Lahdenne	46	case serie	Finland	10	1 (?)	9.3*	?
2003	Quartier	21	open prospective observational	France	61	2.5 (1.1)	76*	mean 6.6
2004/ 2009	Horneff	26, 43	open prospective observational	Germany/ Austria	322/ 604	4 (1.0) (2004)	592/ 1149	median 3.9 (2009)
2004	Hendrickson	42	case serie	USA	8	2 (2.0)	15	mean 4.5/ median 4.4
2005	Kimura	45	survey	USA	82	2.3 (2.1)	167.25*	mean 5.2
2005	Mori	51	open prospective observational	Japan	22	0.3 (0.3)	5.5*	mean 4.7
2009	Prince	27	open prospective observational	Nether-lands	146	6.3 (2.5)	436	median 4.1
2009	Giannini	59	Open partly retrospective/ mostly prospective observational	USA/ Canada	397	3 (2.2)	859.3	mean 3.8

*estimated with reported data, # included patients from the randomized, controlled, withdrawal trial, who did not have a sufficient response to etanercept. Patients were treated with a double dose etanercept, ? unknown, ‡ median instead of mean, mo; months

Subtypes	Age (range)	Mean age at start	Outcome description
sJIA, pJIA and oJIA ext	4-17	10.5	after 3 mo 64% ACR Pedi 50, 36% ACR Pedi 70, after 7 mo patients on ETN 72% ACR Pedi 50, 44% ACR Pedi 70, significant more flares in patients on placebo
sJIA and pJIA	5-32	7.1	decrease of 49% in swollen joint count en 94% in tender joint count, less than 10 min morning stiffness, decrease of 64% in ESR
All, except oJIA persistent and ERA	2.5-9	5.1	sJIA patient did not respond, other 6 immediate decrease in joint pain, disappearance morning stiffness, regression of joint swelling, decrease in ESR
sJIA, pJIA and oJIA ext	5-16	8.4	high dose is safe and well tolerated in JIA, but efficacy seems limited
?	8-18	14	BSR criteria: 4 (67%) achieved a good response, 1 partial and 1 no response.
sJIA, pJIA RF - and oJIA ext	3-15	9.6	excellent clinical response; outcome measures used were ESR, CRP, number of intra-articular glucocorticoid injections and inpatient days needed
sJIA	2-17	9‡	ACR Pedi 30,50, 70 and 90 were recorded in 78%, 62%, 47% and 31% patients, respectively. 18% met the remission criteria.
sJIA, pJIA and oJIA ext	4-17	10.8	after 8 years; ACR Pedi 30, 50, 70, 90 and 100 response rates 83%, 77%, 61%, 41%, 18%
sJIA, pJIA and oJIA ext	3.3-16.3	10.2	after 3 mo 90% ACR Pedi 50, 6 mo 89% ACR Pedi 50, 12 mo 89% ACR Pedi 50
All, except oJIA persistent	4-22	12.2	after 3 mo 73% ACR Pedi 30, 54% ACR Pedi 50, 38% ACR Pedi 70, 12 mo 39% ACR Pedi 30, 35% ACR Pedi 50, 26% ACR Pedi 70
All	2-18	12.6	after 1 mo 67% ACR Pedi 30, 54% ACR Pedi 50, 30% ACR Pedi 70, 3 mo 79% ACR Pedi 30, 61% ACR Pedi 50, 39% ACR Pedi 70, 6 mo 82% ACR Pedi 30, 70% ACR Pedi 50, 50% ACR Pedi 70
ERA (juvenile spondylarthropathy)	12-25	15.9	significant improvement after 2 mo, sustained for 2 years in act joints, Hb, ESR
sJIA (one adult Still)	0.3-17	9.4	45% poor response, 9% fair response, 12% good response, 33% excellent response, 45% reported one ore more flares
sJIA, pJIA and oJIA ext	4-17	11.4	after 12 mo 91% ACR Pedi 30 and 50, 68% ACR Pedi 70
All, except oJIA persistent	0-18	11.2‡	after 3 mo 77% ACR Pedi 30 and in most patients this sustained, 36% of all patients achieved remission
sJIA and pJIA	0-18	10.3	scores for VAS physician and active joint count improved from baseline and improvement was sustained op to 36 mo for those who continued etanercept (n=179)

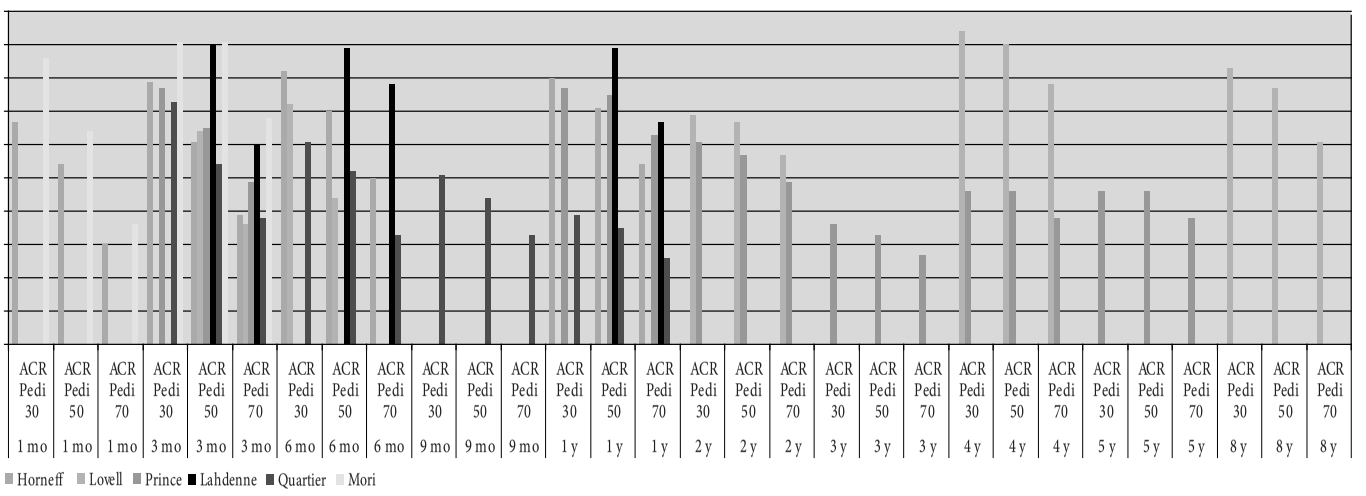

Figure 2.1: ACR Pedi 30, 50 and 70 improvements (see page 225 for color figure)

Horneff (43); based on last observation carried forward (LOCF)

Lovell (13, 48-50); based on LOCF

Prince (27); based on intention to treat analysis (ITT)

Lahdenne (46); based on ITT analysis (only 10 patients included)

Quartier (21); based on ITT analysis

Mori (51); all 22 patients were included in the analysis,

Mo; months, Y; years

Table 2.3: Effectiveness etanercept per JIA subtype

JIA subtype	Effectiveness
sJIA*	Subject of discussion; success rates vary between studies but clearly more patients discontinue due to ineffectiveness compared to other subtypes.[21,27,38,39,43,45,49,52] However, the ones who continue etanercept show equal effectiveness on the long-term.[27,60] Other cytokines such as IL-1, IL-6 and IL-18 may play an important role.[63,64]
pJIA RF +*	Good and rapid clinical response, which is sustained on the long-term. Chance of successful discontinuation of etanercept in case of remission seems low.[65] Patients should be started on etanercept early in disease course.[7]
pJIA RF -*	Good and rapid clinical response, which is sustained on the long-term. Better improvement in combination with MTX.[26]
oJIA ext*	Good and rapid clinical response, which is sustained on the long-term.[21,27]
oJIA pers	Very limited data, since etanercept is recommended for polyarticular course JIA only.[26,43]
ERA	Major improvement with monotherapy etanercept.[26,42,56] Case report on radiological remission at 2 years.[56]
PsJIA	Good and rapid clinical response (more than 80%) on arthritis and psoriatic leasions, which is sustained, but data is limited.[27,43]
uJIA	Very limited data.[26,43]

*Efficacy tested in randomized controlled trial

Three studies evaluated growth in JIA patients during etanercept therapy.[72-74] All demonstrated catch-up in growth during treatment. Tynjälä et al. reported on 43 JIA patients in whom change in inflammatory activity was the most significant predictor of the growth velocity (even when taking decrease in glucocorticoid dose into account).[72] Vojvodich et al. studied 20 prepubertal and 11 early/midpubertal patients who used etanercept for at least one year and found a growth improvement independent of the pubertal growth spurt.[73] The need for intra-articular glucocorticoid injections was negatively correlated to the improved growth. Schmeling et al. suggested that the beneficial effect of etanercept on growth might be related to the cessation of the inhibitory effect of proinflammatory cytokines on the synthesis of IGF-1 and IGF-BP-3 in the liver.[74] The authors also state that growth failure should be included in the evaluation of anti-rheumatic treatment.

Osteopenia or osteoporosis is a major complication of Juvenile Idiopathic Arthritis. Simonini et al. prospectively enrolled 20 JIA patients before start of etanercept therapy, after 12 months 15 were considered responders (ACR Pedi 50 improvement).[75] The responders differently from the non-responders, showed a significant increase in both broadband

ultrasound attenuation and Z-score values. Studies in larger patient groups need to confirm these data.

Health-related quality of life (HRQoL)

Three studies report specific on changes in HRQoL in JIA patients treated with etanercept. Investigators from the USA have collected the disease specific Childhood Health Assessment Questionnaire (CHAQ), the disease specific Juvenile Arthritis Function Assessment Report (JAFAR) and the generic Pediatric Quality of Life Inventory Version 4 (PedsQL Generic Scale) in 21 children with sJIA and pJIA.[76] Patients who already started therapy were instructed to think back on their quality of life and function prior to start of etanercept. All scales improved during etanercept treatment in both the sJIA as well as the pJIA patients, indicating improvements in functional status, emotional well-being, quality of life and activity level. However, recall bias might have played a role and this makes outcomes questionable.

The functional aspect of HRQoL and its determining factors during etanercept therapy were investigated by Halbig et al.[60] Outcomes of the disease specific CHAQ from 114 JIA patients over a period of 2 years were analyzed. Patients had poor functional ability and high disease activity. Under etanercept therapy dramatical improvements of functional ability were found in patients of all JIA subtypes within 6 months of treatment and improved further up to 24 months. Disease activity decreased accordingly.

There is only one prospective study, which evaluates the HRQoL on all aspects. In 53 Dutch JIA patients (of all subtypes except oJIA pers and uJIA) HRQoL was measured by the disease specific CHAQ, and the generic Child Health Questionnaire (CHQ) and Health Utilities Index mark 3 (HUI3) at start and after 3, 15 and 27 months of etanercept treatment.[77] At the same time points the remaining response variables of the JIA core set were collected. Significant improvements were shown after three months on both disease specific and generic HRQoL outcomes and these improvements continued at least up to 27 months of treatment. The disease specific CHAQ, including VAS pain and well-being, showed a significant improvement on all domains. The generic health-profile measure CHQ improved on all the health concepts impaired by JIA except for "general health". The generic preference-based HUI3 showed impairment and subsequently significant improvement on the more specific domains ("pain", "ambulatory", "dexterity"). In accordance also disease activity variables improved significantly over time.

All three studies indicate that etanercept is not only effective in reducing disease activity in JIA patients, both it also has a positive effective on HRQoL in all aspects affected by JIA. Since severe JIA frequently results in physical disabilities and chronic pain influencing daily life, this is a highly relevant finding.[4,5]

JIA associated uveitis

Between 5-25% of JIA patients will develop uveitis; most commonly patients with oJIA.[78,79] Uveitis can lead to cataract and even blindness.

Several studies describe newly onset or flaring of JIA associated uveitis during etanercept therapy.[21,26,41,80,81] However, a large survey study, as well as a large chart review study, showed that there was no significant increase in uveitis in patients on etanercept compared to patients not on etanercept.[82,83] Also, severity of uveitis deed not seem to be influenced by etanercept.

Controversy, there are also reports on the therapeutic effect of etanercept on uveitis. A small prospective study in 16 eyes showed a statistically significant improvement in 63%.[84] Increase of the etanercept dose did not have an added improvement effect. A double-blind RCT of 12 patients did not detect differences in uveitis between the placebo and etanercept treated group, but power was low.[85]

Etanercept may benefit certain patients with JIA associated uveitis, but appears more effective in treating the arthritis than the uveitis. Several studies showed a better effect of infliximab and adalumimab on active uveitis compared to etanercept.[86-89]

Macrophage Activation Syndrome (MAS)

Patients with sJIA have a propensity to develop MAS. This is a potentially fatal hemophagocytic syndrome, which can be triggered by medication or infection.[90,91] Etanercept has been described as both as a treatment as well as a trigger for the development of MAS. Ramanan et al. described a patient with sJIA who developed MAS after 4 doses etanercept.[92] Kimura et al. report two patients who developed MAS after 12 and 25 months of etanercept use during a disease flare.[45] Several case reports describe sJIA patients with therapy-resistant MAS, who were successfully treated with etanercept.[93-95] More understanding of the pathogenesis of MAS is needed.

Safety

SAE/AE

Literature reports over more than 3250 patient-years of experiences in treating JIA patients with etanercept (table 2.4). All SAEs and AEs reported until now are listed in table 2.5 and 2.6. Frequencies are not always given, therefore is not possible to give exact numbers but it is clear that the most common reported AEs are injection side reactions and infections.

AE-rates vary from 0.08 to 20.2 per patient year. SAE-rates vary from 0.018 to 0.12 per patient year (table 2.4). Most reported SAEs are severe infections, neurological or neuropsychological disorders and autoimmune diseases. Only a small portion (approximately 5%) of patients discontinues etanercept due to (S)AE.[21,26,27,43,49]

Tolerability of etanercept was first described in 69 patients in a randomized, controlled withdrawal trial by Lovell et al.[13] Two patients were hospitalized for SAE; one depression and a personality disorder and one for gastroenteritis-fly syndrome. One patient withdrew etanercept because of urticaria, but later etanercept was reintroduced without recurrence. All other AEs ware mild to moderate.

One study from Italy focused on AEs in 127 JIA patients while treated with etanercept. Over a 6-year period 133 AEs occurred in 69 patients (total AE-rate 0.52 per patient year).[96] They reported a higher number of patients (14%) discontinuing etanercept due to AE than other studies.

There are no significant differences in SAE-rate between JIA subtypes reported, although there is slightly higher occurrence of SAE in sJIA patients compared to other subtypes.[96]

Several observational studies have reported on the safety of etanercept, these are listed in table 2.4. Due to the design of these types of studies, it is likely AEs are underreported compared to controlled clinical trials and specific safety studies. SAEs and AEs described in case reports and case series are admitted in table 2.5 and 2.6.

No deaths during use of etanercept have been reported. The Dutch national register reports three deaths (TB, MAS, sepsis) after discontinuation of etanercept for at least 8 months.[27] These three sJIA patients had an uncontrolled disease despite multiple immunosuppressive agents.

Injection site reactions

Injection site reactions are the most common reported AEs (28-39%) and most likely a T-lymphocyte mediated delayed-type hypersensitivity reaction which will self-resolve due to tolerance.[81]

Infections

The immunosuppressive features of etanercept make patients more susceptible for infections. These vary from minor to very serious and life-threatening infections. Opportunistic infections such as tuberculosis (TB) and listeriosis are especially feared. There are guidelines for TB screening before start of etanercept.[22] Incidence of TB is lower during etanercept therapy compared to infliximab treatment.[58,97] Varicella infection can be severe in patients treated with etanercept.[26,43,48,50] Since non-immune JIA patients treated with etanercept can not be vaccinated, parents should be instructed about what action to take if their child comes into contact with varicella.[98]

Lovell et al. reported 0.03 medical important infections per patient year over an 8-year period, with no increase over time.[49] These infections included pyelonefritis, peritonitis and appendicitis, acute varicella infection, aseptic meningitis secondary to varicella infection, soft tissue infection, post-operative wound infection, sepsis requiring amputation of foot, dental abscess and gastrointestinal infection.

Neurological or neuropsychological disorders

A large number of neurological or neuropsychological disorders have been reported during etanercept use (table 2.5 and 2.6), especially headaches. It should be noted that headaches in general are common in childhood.[125] The Italian safety study however reported that severe headache, unusual aggression and pain application syndrome seemed to be dose dependent.[96]

TNF is thought to play a role in the pathogenesis of inflammatory demyelination disease of the central nervous system, potentially putting children treated with etanercept at a higher risk.[126] Two cases of demyelination in JIA patients on etanercept are reported until now.[43,127] In addition, four JIA patients treated with etanercept developed optic neuritis.[101,113] Three out of four patients had a history of JIA-associated uveitis, but their ocular disease was well controlled before start of etanercept therapy.

Table 2.4: Reports on the safety of etanercept, reporting more than 5 patients

Year	Author	Ref no.		Country	No. of patients
2000	Lovell	13	3 mo open label, followed by 4 mo double-blind RCT	USA	69
2001/2002	Kietz	57, 58	open prospective observational	USA	22
2001	Schmeling	53	case serie	Germany	7
2001	Takei	38	retrospective chart review	USA	8
2002	Cairns	40	open prospective observational	Northern Ireland	6
2002	Haapasaari	41	retrospective collected data	Finland	31
2002/2009	Russo	39, 52	open prospective observational	Argentina	45
2003/ 2006/2008	Lovell	48-50	open label extension	USA	43/34/26
2003	Lahdenne	46	case serie	Finland	10
2003	Quartier	21	open prospective observational	France	61
2004/2009	Horneff	26, 43	open prospective observational	Germany	322/604
2004	Hendrickson	42	case serie	USA	8
2005	Kimura	45	survey	USA	82
2005	Mori	51	open prospective observational	Japan	22
2008	Gerloni	96	open prospective observational	Italy	127
2009	Prince	27	open prospective observational	Nether-lands	146
2009	Giannini	59	open part retrospective/ part prospective observational	USA/ Canada	397

* estimated with published data, ? unknown

sJIA; systemic JIA, pJIA; polyarticular JIA, oJIA; oligoarticular, ext; extended, pers; persistent, ERA; enthesitis-related arthritis, MII; medical important infections, ETN; etanercept, MTX; methotrexate.

No. of patients-years	Subtypes	Age (range)	Serious Adverse Events		Adverse Events	
			No. of events	No. of events per patient-year	No. of events	No. of events per patient-year
40.3*	sJIA, pJIA and oJIA ext	4-17	2	0.05	not reported	
367.4	sJIA and pJIA	5-32	0	0	not reported	
3	All, except oJIA pers and ERA	2.5-9	0	0	2	0.667
10.1	sJIA, pJIA and oJIA ext	5-16	0	0	4	0.396
12*	?	8-18	0	0	1	0.08
28.8*	sJIA, pJIA and oJIA ext	3-15	1	0.035	not reported	
121.2	sJIA	2-17	not reported (0 until 2002)		4 (until 2002)	
107/225/ 318	sJIA, pJIA and oJIA ext	4-17	39	0.12	9 (MII)	0.03
9.3*	sJIA, pJIA and oJIA ext	3.3-16.3	not reported		not reported	
76*	All, except oJIA persistent	4-22	12	0.16	55	0.72
592/ 1149	All	2-18	12/ 52	0.020/ 0.045	57/ 190	0.096/ 0.165
15	ERA (juvenile spondylarthropathy)	12-25	0	0	not reported	
167.25*	sJIA	0.3-17	3	0.018	29	0.17
5.5*	sJIA, pJIA and oJIA ext	4-17	0	0	111	20.2
258	All	1.9-49.8	19	0.074	133	0.515
436	All, except oJIA pers	0-18	9	0.029	56	0.179
859.3	sJIA and pJIA	0-18	54	0.071 (ETN)/ 0.060 (ETN+MTX)	179	0.187 (ETN)/ 0.216 (ETN+MTX)

Table 2.5: Reported SAEs

SAEs	Ref number
Severe infections	
Herpes zoster	26, 43, 59
Hip prosthetic infection	96
Listeria monocytogenes infection	99
Multifocal septic arthritis and osteomyelitis by group A streptococcus	100
Pancytopenia	21
Postoperative wound infection	48, 50
Sepsis (including amputation left foot)	48-50
Septic abscess	59, 103
Septic arthritis	26, 43
Soft tissue infection	26, 43
Soft tissue infection after cut to the hand	48, 50
Unspecific infections (prolonged or with fever)	26, 43
Urosepsis	27
Varicella-zoster virus infection	26, 43, 48, 50, 59
Allergic reaction	
Allergic reaction	49
Stevens-Johnson syndrome	26
Auto-immune disorder	
Diabetes Mellitus Type 1	8, 48, 50, 59
Macrophage activation syndrome	21, 45
Pancytopenia	21
Raynaud's phenomenon	59
Sarcoidosis	27
Severe thrombocytopenia and leucopoenia	96
Systemic lupus erythematosus	106, 107
Type 1-autoimmune hepatitis	108
Vasculitic skin rash and systemic symptoms	21
Vasculitis	109-111
Respiratory tract disorders	
Life-threatening bacterial pneumonia	96
Pneumonia	26, 43
Upper respiratory tract infection	26, 43

Table 2.5: Continued

SAEs	Ref number
Gastrointestinal disorders	
Appendicular abscess	21
Aspecific inflammatory bowel disease	96
Colicky cholelithiasis	26
Colitis	59
Colitis ulcerosa	27
Crohn's disease	21, 26, 27, 96, 116, 117
Epigastric and abdominal pain	48, 50
Epigastric pain	48, 50
Gastroenteritis	26, 59
Gastroenteritis-flu syndrome	13
Peritonitis/ appendicitis	48, 50
Urinary tract disorders	
Elevated serum creatinine	26
Infection of urachal cyst	118
Mycobacteria tuberculosis peritonitis	119
Painful urination	26
Pyelonephritis	49
Urinary tract infection	26, 43
Gonadal disorders	
Ovarial cyst bleeding	26
Eye disorders	
Papilitis	26
Retrobulbar optic neuropathy	21
Uveitis flare	21, 41, 59, 96, 101, 102
Uveitis new onset	26, 59, 82, 104
Skin or nail disorders	
Psoriasis	15
Skin lesions	26, 43
Toxic epidermial necrolysis	43
Circulation or hematologic disorders	
Myocardial dysfunction and pericarditis during flare	45

Table 2.5: Continued

SAEs	Ref number
Neurological or neuropsychological	
Acquired sensorineural hearing loss	105
Anorexia nervosa	96
Cervical subluxation and aseptic meningitis (after infection with VZV)	48, 50
Demyelization	26, 43
Depression	96
Depression and personality disorder	13
Epileptic insult	27
Headaches	59
Headaches and marked dysesthesia	21
Hearing loss	26
Hypoglossal paralysis	96
Multiple sclerosis	112
Neuroalgodistrofy	96
Optic neuritis	101, 113
Panic attacks and anxiety	96
Peripheral neuropathy	59
Reflex sympathetic dystrophy	59
Seizures	26, 43, 44
Severe psychiatric disorder	21
Malignancies (number of cases reported)	
Hodgkin's lymphoma (4)	114, 115
Non-Hodgkin's lymphoma (1)	26
Thyroid carcinoma (2)	26, 43, 96
Yolk sac carcinoma (1)	26
Miscellaneous	
Arthralgia	49
Aseptic necrosis of femoral head	96
Dental abscess	48, 50
JIA flare	26, 49, 59
Major weight gain	21
Osteochondritis dissecans	26

Table 2.6: Reported AEs

AEs	Ref number
Injection side reactions	13, 21, 26, 27, 38, 39, 42, 43, 45, 51, 53, 57, 58, 76, 81, 96
General infections	45
Abscess	59
Acute viral sundrome	59
Blood culture-positive bacteremia	59
Dental infection	26
Epstein-Barr virus infection	27, 96
Febrile seizure	43
Fever	26, 27, 43, 44, 48
Flu-syndrome	48, 76
Fungal infection	26
Herpes labialis	26, 43
Herpes zoster	26, 27, 43, 59
Lymphadenopathy	27, 43
Pharyngitis	59
Pilonidal cyst infection	59
Postappendectomy wound infection	59
Pyelonephritis	59
Scarlet fever	96
Soft tissue infection	26
Urosepsis	59
Varicella-zoster virus infection	26, 48, 96
Allergic reaction	45
Allergic conjunctivitis	43
Urticaria	13, 41, 43, 45, 121
Respiratory tract disorders	
Bronchial asthma	96
Bronchitis	59
Colitis (clositridium difficile)	59
Chronic cough	21, 27, 44
Rhinitis	13, 38, 48, 51
Rhinorrhea	44
Upper respiratory tract infection	13, 21, 26, 27, 43, 48, 96

Table 2.6: Continued

AEs	Ref number
Gastrointestinal disorders	21
Abdominal or epigastric pain	96
Abdominal pain	13, 26, 27, 43, 48, 51
Aseptic bowel inflammation	96
Biliary calculosis	96
Diarrhea	26
Gastrointestinal infection	13, 27, 40, 51, 59, 96
Helicobacter gastritis	96
Nausea	13, 26, 27, 39, 43, 48
Oesophagitis	43
Oral aphtosis	96
Pharyngitis	13, 38, 48, 51
Proctorrhagia	96
Vomiting	13, 26, 27, 39, 43, 51
Urinary tract disorders	
Cholecystitis (sterile)	43, 122
Hypercalcuria/ kidney stones	45
Unexplained macrohaematuria	96
Urinary tract infection	26, 59, 96
Gonadal disorders	
Gonadal pathologies (ovarian cyst, endometriosis)	96
Irregular / painful menses	96
Eye disorders	
Conjunctivitis	48
Uveitis	26
Ear disorders	
Infection ear lobe	27
Otitis	27, 48
Circulation or hematologic disorders	
Epistaxis	96
Extrasystolia	96
Hypertension	96
Tachycardia	96

Table 2.6: Continued

AEs	Ref number
Skin or nail disorders	
Atopic dermatitis	120
Cutaneous leg ulcer	96
Eczema	43
Impetigo	96
Impetigo contagiosa	43
Micotic vaginitis	96
Multiple mollusca contagiosa	43
Onychodistrophy	96
Pityriasis versicolor	96
Pruritic, urticarial rash	96
Rash	13, 21, 26, 27, 41, 43, 48, 51
Skin changes	26
Skin infection	48
Vertigo	96
Neurological or neuropsychological	26
Aggressiveness	96
Concentration disorder	27, 96
Headache	13, 21, 26, 27, 43, 45, 48, 51, 96
Hyperalgesia	96
Mild mood changes	21
Nervousness/ hyperactivity	96
Pain amplification syndrome	96
Laboratory abnormalities (including raised liver enzymes, leucocytopenia, thrombocytopenia)	26, 43, 59, 96
Monoclonal electrophoretic band	96
Miscellaneous	
Accidental injury	48
Alopecia	96
Anorexia	21
Asthenia	21
Coccigeal cyst	96
Dizziness	43
Fatigue	27, 45, 96

Table 2.6: Continued

AEs	Ref number
Miscellaneous	
Hair loss	26, 27, 43, 106
Hematoma	21
JIA flare	26, 44
Joint effusion	59
Myalgias	45
Osteoporosis	27
Pregnancy	21, 123
Sleeplessness	43, 106
Thoraric pain	21
True thymic hyperplasia and mediastinal lymphadenopathy	124
Weight loss	27

Malignancies

An increase in malignancies has been a concern as a possible long-term effect of etanercept and other TNF-blocking agents. The United States Food and Drug Administration (FDA) has given out a warning in 2008 about the possible association between the use of medicines known as tumor necrosis factor (TNF) blockers and the development of lymphoma and other cancers in children and young adults.[128] In 2009 they reported their analysis of tumor necrosis factor (TNF) blockers and concluded that there is an increased risk of lymphoma and other cancers associated with the use of these drugs in children and adolescents.[129] In total the FDA claims to have found 14 cases of malignancies in JIA patients using TNF-alpha blocking medicine, of which we could trace back 13 as summarized in table 2.7.[130] Not enough details were given to report of differences in JIA subtype. No dose association was found. It was estimated by the FDA that 9,200 children ages 0-17 years received etanercept through December 2007 (source Amgen).[130] The background incidence of malignancy in JIA patients is not well defined. In RA an increased risk of lymphoma is observed.[131,132]

We found 8 cases of malignancies reported in JIA patients during or after etanercept use (table 2.5) in the literature. It is unclear exactly which cases were also reported by the FDA.

The incidence of malignancies in the German registry (0.26/100 patient years) was higher compared to the incidence in the total German population (0.0147/100 patient years in

children below the age of 15 years).[26] However, the authors mention that this finding must be interpreted with caution since the three cases from the German registry cannot be easily attributed to treatment with etanercept and two of the patients were older than 15 years.

The strength of the association between etanercept use and risk of developing a malignancy in JIA patients is subject of further investigation.

Table 2.7: Malignancies in JIA patients who used etanercept as reported to the FDA

Country and source	Adverse event	Age at event (years)	Time from etanercept to onset	Indications	Comments/ confounders
USA; Healthcare professional	Leukemia	10	5 months	pJIA RF-	-
German registry	Diffuse large B-cell lymphoma	14	7 years	JIA	MTX
USA; Healthcare professional	Hodgkin's disease(lymphoma)	15	3.6 years	JIA	MTX
Germany; Health-care professional	Acute lymphocytic leukemia	Child (un-known age)	approximately 1 year	sJIA	MTX
Germany; Health-care professional	Acute lymphocytic leukemia	Child (un-known age)	Report of "a few months"	uJIA	MTX
German registry	Yolk sac tumor site unspecified	16	29 days	JIA	1 month MTX
Great Britain; Health care professional	B-cell lymphoma	18	3 years	JIA	-
USA; Healthcare professional	Acute myeloid leu-kemia, lymphoma	19	1.5 years	ERA	Smoker, family history of breast cancer, colon cancer
British registry	Malignant mela-noma	19	11 months	psJIA	MTX, etanercept initiated at age 18 years 3 months
Great Britain; Health care professional	Malignant mela-noma	19	14 months	psJIA	
USA; Healthcare professional	Papillary thyroid cancer	18	4 years	JIA	Confirmed by biopsy
German registry	Thyroid cancer	18	10 months	ERA	Diagnosis con-firmed MTX co-suspect
German registry	Myelodysplastic syndrome	17	4 years	JIA	Considered panctopenia after medical review due to myelosuppres-sive therapy

New onset autoimmune diseases

There are several reports of autoimmune diseases occurring or flaring in JIA patients during etanercept treatment. The occurrence of Crohn's disease and collitis ulcerosa was unexpected, considering anti-TNF-alpha is also successfully used to treat these diseases.[133,134] There are also reports on demyelination, sarcoidosis, vasculitis, systemic lupus erythematosis (SLE) and diabetes mellitus type 1 (table 2.5). The question is whether there is a causal link between etanercept use and the occurrence of these illnesses or if it is more associated with having Juvenile Idiopathic Arthrtitis. Without knowing the rate of coexistence of autoimmune disorders in the population, it is difficult to establish whether this occurrence is an adverse effect of etanercept or simply the expected development of multiple autoimmune diseases within the same person.[135]

It is recommended that clinicians should remain alert for clinical evidence of development of new autoimmune disease and check laboratory titers of antibodies in case of suspicion.[98] Especially when there is a positive family history of autoimmunity.[136]

Use

Etanercept is recommended for the use in JIA patients with a polyarticular course, who have had an inadequate response to the maximum (tolerated) dose of MTX.

Checks before starting (contraindications)

The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Before start of etanercept, patients should be checked for presence of contraindications as listed in table 2.8.[22]

Table 2.8: Contraindications for the use of etanercept[22]

Young women who are pregnant or breastfeeding or who are sexually active with inadequate contraception
Active infection
Current or previous tuberculosis
Previous or present sepsis of a prosthetic joint still in situ
Malignancy or pre-malignancy states
Immunodeficiency

Etanercept should be withdrawn in the event of malignancy, severe drug related toxicity or temporary withdrawal in case of severe intercurrent infection.

There have been concerns regarding use of etanercept or other TNF-blocking agents during pregnancy. Although not applicable to most paediatric patients, there have been reports on pregnancies in JIA patients on etanercept.[21,59,123] Etanercept is classified as Category B with regard to use during pregnancy (no harm to fetus reported in animal studies, but no well-controlled studies have been conducted in pregnant women; therefore should be used during pregnancy only if clearly needed).[137]

Immunization in JIA with live vaccines is a safety issue and data are limited.[22] A study on efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept by Borte et al., showed that etanercept treatment does not seem to interfere with intended outcome of this revaccination in children with JIA.[138]

Patients under 4 years old

Etanercept has not been registered in Europe for use in JIA patient under the age of 4 years. In the USA it is registered for children older than 2 years of age.[22,139] In the German registry 25 JIA patients under 4 years old were described.[26] A relatively large portion of these patients had sJIA (60%) and were more frequent treated with corticosteroids and MTX compared to the patients in the registry above the age of 4. This indicates a more severe disease course, however surprisingly no differences in effectiveness were shown between groups. In the young children only 2 AE and no SAE were reported. Also, reports from other studies show no problems treating children younger than 4 years with etanercept although no specific analyses are described.[27,39,41,45,46,52-54]

Discontinuation of etanercept in JIA patients

Discontinuation of etanercept can have several reasons (table 2.9). Considering possible (S)AEs on the long-term, the high cost and the burden of weekly injections it is desirable to discontinue etanercept therapy as soon as the patient is either in remission or if it is clear that etanercept therapy is ineffective.

Patients in remission (or their parents) may be reluctant to discontinue etanercept since they do not want to risk a disease flare. Only one study tried to answer the questions when and how to stop etanercept after successful treatment of JIA patients.[65] Of the 17 patients 9 (53%)

reported sustained remission after discontinuation. Those children were longer in remission according to the Wallace criteria prior to discontinuation compared to the patients who experienced a flare. Four out of five children who discontinued etanercept without tapering flared. Authors recommend patients to meet the criteria of CRM for at least 1.5 years before considering discontinuation and taper the etanercept carefully. Also, the National Institute for Clinical Excellence (NICE), UK, recommend in their guidelines a 2 years disease-free period before discontinuation of etanercept.[22]

Patients who do not improve on etanercept within three months of treatment, discontinue its use in most cases.[21] However, Lovell et al. reported on a number of patients who continued therapy in spite of initial inefficacy and who showed a delayed response. A paper from the Dutch national register showed that more than half of the intial non-responders (according to the ACR Pedi 30) did respond after prolonged treatment.[140]

Costs

Etanercept is a relatively expensive treatment, however it possibly can prevent long-term disability and reduce the burden on both patients and society. A study from Finland evaluated the costs of adding etanercept to the prevailing drug therapy in 31 JIA patients during a one-year period.[141] These patients were refractory to conventional DMARDs. Overall direct cost (costs within health care) increased $4200 per year, but indirect costs (costs outside of health care related to the disease) decreased $1700 per year, with resulted in a total increase of cost of 10% per patient per year. Direct costs increased the most in the first 3 months of treatment but decreased later on The authors stress that this slight increase should be seen in light of the reduced inflammatory activity and the probable reduction of lifetime pain and disability caused by refractory JIA.[141]

A cost-utility analysis (CUA) was undertaken as part of the manufacturer's submission.[142] The model is based on a model for RA and contains a large number of assumptions. For a patient started on etanercept rather than placebo, the incremental benefit estimated per person was 1.74 quality adjusted life year (QALY). Cost per QALY was £16,082 (range £3,900 - £34,000). Considering the weaknesses of the model, the validity and accuracy of this estimated is questionable.

Table 2.9: Discontinuation of etanercept

Year	Author	Ref no.	Patient years	Stop due to remission	Stop due to unsuccessful use	Reasons unsuccessful use
2000	Lovell	13	40.3*	0	11 (16%)	Ineffective, AE, refusal, flare
2001/ 2002	Kietz	57, 58	30.8*	1 (5%, pJIA RF+, flared)	none	
2001	Schmeling	53	3*	0	1 (1%)	Ineffective
2001	Takei‡	38	10.1	0	6 (75%)	Ineffective, flare despite high dose
2002	Cairns	40	12	0	1 (17%)	AE (temporarily)
2002	Haapasaari	41	28.8*	0	5 (16%)	Ineffective, AE, difficulties carrying out injections at home
2002/ 2009	Russo	39, 52	121.1	5 (11%, not clear if on ETN)	22 (49%)	Ineffective, flare
2003/ 2006/ 2008	Lovell	48-50	107/ 225/ 318	0	38 (66%)	Ineffective, AE, refusal, flare, physician decision, protocol issue, LTFU, other
2003	Lahdenne	46	9.3*	0	1 (10%)	non-compliance
2003	Quartier	21	76*	1 (2%)	29 (48%)	Ineffective, intolerance, flare, pregnant
2004/ 2009	Horneff	26, 43	592/ 1149	14 (4%, 7 flared within 1-11 mo)/ 6 (1%)	39 (12%)/ 59 (10%)	Ineffective, SAE/AE, patients withdraw, LTFU
2004	Hendrickson	42	15	0	1 (13%)	LTFU
2005	Kimura	45	167.25*	3 (4%)	26 (32%)	Poor response, flare or poor compliance, AE
2005	Mori	51	5.5*	0	1 (5%)	Joint contracture
2008	Gerloni	96	127	not reported	18 (14%)	SAE/AE (safety study)
2009	Prince	27	146	8 (5%)	33 (23%)	Ineffective, SAE/AE, flare
2009	Giannini	59	397	20 (5%)	198 (50%)	Ineffective, AE, refusal patient or parent, protocol issue, physician decision, other

*Estimated with reported data

‡Patients evaluated in this study received a dose of 0.8 mg/kg twice weekly because they previously did not respond to the usual dose.

LTFU; lost-to-follow-up

Response to etanercept after use of other biologicals

Since etanercept was the first registered biological for JIA, most patients were biological naïve before the start of etanercept. Therefore, little is known about the success rate of treating patients with etanercept after other biologicals were ineffective.

In Italy 32 patients who were unsuccessfully treated with infliximab, were switch to etanercept. However, the study was designed to report adverse events and therefore no data on effectiveness were described.

Biomarkers response

Currently there are no reports on biomarkers that able to predict response to etanercept.

CONCLUSION

This review summarizes clinical data from the literature on experiences with etanercept in JIA since it was registered a decade ago.

Efficacy and tolerability was tested in one randomized controlled study. Several longitudinal studies have shown that etanercept (either in the dose of 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly) is able to rapidly reduce disease activity with sustained effect in a great part of the JIA patients, who were previously refractory to synthetic DMARDs. However, especially short-term effectiveness is dependent of JIA subtype, sJIA patients being less responsive. In most patients concomitant medication could be discontinued.

Of all biologicals, by far most experiences in JIA patients are with etanercept, since it had been the only registered biological for JIA from 1999 till 2008. Etanercept is still considered first choice biological for most JIA patients, however, choice of biological is disputable for sJIA patients and patients with JIA associated uveitis. Etanercept is not registered for patients under 4 years old in Europe and under 2 years old in USA, but is reported to be effective and safe for these patients group. Although overall etanercept has a good safety profile, SAEs such as malignancies and serious infections cause concerns. Most common AEs are injection side reactions and infections. It is important to check patients for infections before starting etanercept but also during therapy.

Major improvements in health-related quality of life were measured in JIA patients during the use of etanercept. The costs for etanercept seem reasonable, considering the major improvement in health status.

Registries will keep provide important information on the long-term effectiveness and safety of etanercept.

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Part 2

Methods

Chapter 3

Developing an effective and safe method for multicenter data collection

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Development of a web-based register for the Dutch national study on biologicals in Juvenile Idiopathic Arthritis: www. ABC-register.nl
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ABSTRACT

Objectives: Most clinical studies use paper case record forms (CRFs) to collect data. In the Dutch multicentre observational study on biologicals we encountered several disadvantages of using the paper CRFs. These are delay in data collection, lack of overview in collected data and difficulties in obtaining up-to-date interim reports. Therefore, we wanted to create a more effective method of data collection compared to CRFs on paper in a multi-centre study.

Methods: We designed a web-based register with the intention to make it easy to use for participating physicians and at the same time accurate and up-to-date. Security demands were taken into account to secure the safety of the patient data.

Results: The web-based register was tested with data from 161 Juvenile Idiopathic Arthritis patients from nine different centres. Intern validity was obtained and user-friendliness guaranteed. To secure the completeness of the data automatically generated email alerts were implemented into the web-based register. More transparency of data was achieved by including the option to automatically generate interim reports of data in the web-based register. The safety was tested and approved.

Conclusion: By digitalizing the CRF we achieved our aim to provide easy, rapid and safe access to the database and contributed to a new way of data collection. Although the web-based register was designed for the current multi-centre observational study, this type of instrument can also be applied to other types of studies. We expect that especially collaborative study groups will find it an efficient tool to collect data.

INTRODUCTION

Biologicals are a recent development in the treatment of Juvenile Idiopathic Arthritis (JIA).[1-5] The efficacy and safety of etanercept and other biologicals (infliximab, adalimumab and anakinra) is, since the introduction in the Netherlands, investigated in a prospective observational study.[6] This nation-wide survey is coordinated by the Erasmus MC Sophia Children's Hospital in Rotterdam and based on collaboration of the "Arthritis and Biologicals in Children" (ABC) working group members. As result of this collaboration all Dutch JIA patients treated with biologicals since 1999 are included.

Data were documented by the treating physician on paper case record forms (CRFs). The investigator had to collect the CRFs at the local centres and import the data into a database. In time, data collection became more difficult because of the rapidly increasing group of patients using etanercept and the increased use of other biologicals. As data accumulate, lack of overview may occur and as a result side-effects of medication and significant events may remain underreported.[7,8]

In contrast to paper CRFs, a web-based register is a tool to collect data on a long-term continuous basis with more accurateness and completeness.[8] Since a web-based register is thought to be more up-to-date and less time-consuming, data can be collected with the shortest possible delay and lower costs in the long-term.[8-10] In addition, it creates an opportunity for interim reports.

The aim of the web-based register is to provide easy and safe access to the database for the participating physicians, which also produces automatically generated interim reports, and provides an accurate and up-to-date database for the investigators.

METHODS; WEBDESIGN AND STRUCTURED DATA ENTRY

Data collected in the ABC-register

The data collected in the register include patient and disease characteristics as: date of birth, gender, length, weight, onset of the disease, JIA onset type, medical therapy in the past and current co-medication (NSAIDs, glucocorticoids and DMARDs). Furthermore, detailed data are collected regarding the use of biologicals (type, dose, frequency), disease activity conform the JIA core set of response variables and adverse events.[11]

All treating physicians are defined as 'users', the investigators from the coordinating centre are defined as 'investigators'. On conforming to the study protocol, data will be collected at fixed follow-up moments. The users are invited by an automatically generated e-mail message to assure the data collection at each follow-up moment. In case of unforeseen events such as side-effects or disease flaring, the users are asked to add the data on their own initiative.

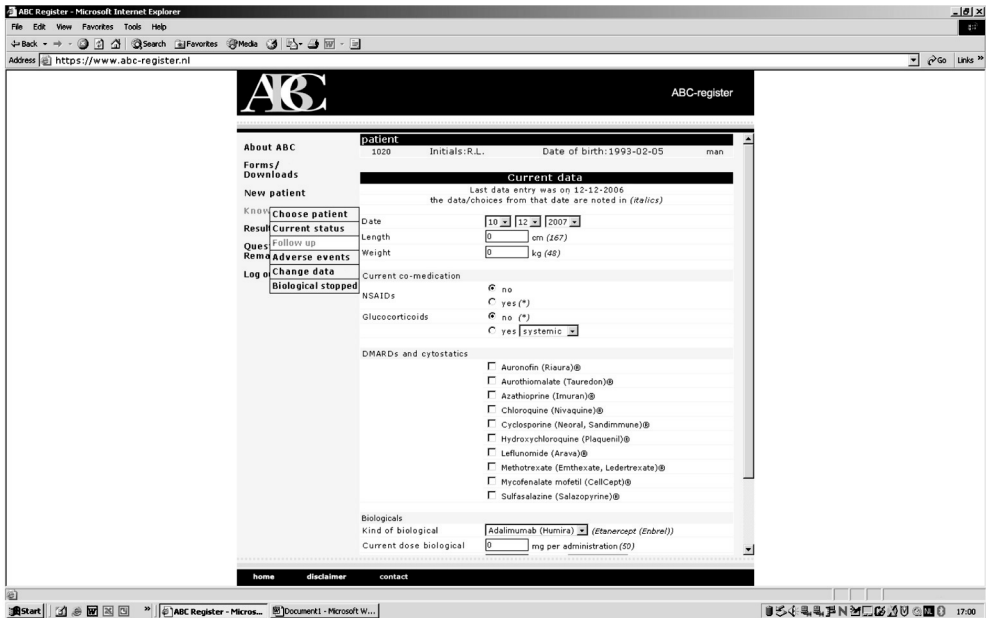

Figure 3.1: Screenshot 1 (translated into English for publication) (see page 226 for color figure). Entering and retrieving data; the upper left side of the screen shows the menu, in which the user can choose the options 'About ABC', 'Forms/ Downloads', 'New patient', 'Known patient', 'Results', 'Questions/ Remarks' or 'Log out'. The right side of the screen displays an entry form for follow-up data. The imported data from the last follow-up for this patient are shown in brackets and italic font style on the screen as a reminder for the user.

Web-based register design

The screens used in the web-based register are presented in a logical sequence. The user logs in to the administrative section, and is then offered different selection buttons from the menu. With the button 'new patient' the user enters the initial data. Under 'known patients' the user has several options besides entering the usual follow-up data, such as reporting adverse events or disease flaring. With the button 'results', an overview is shown of the combined general information of all patients included nation-wide as well as a summary of the specific data of the centre that has logged in. This summary includes the total number of patients included, division in JIA subtypes, gender distribution, the outcome of the JIA core set, reported side-effects and a Kaplan-Meier curve on the continuation of use of the diverse biologicals. The button 'current status' presents a summary of a specific patient (figure 3.1 and 3.2).

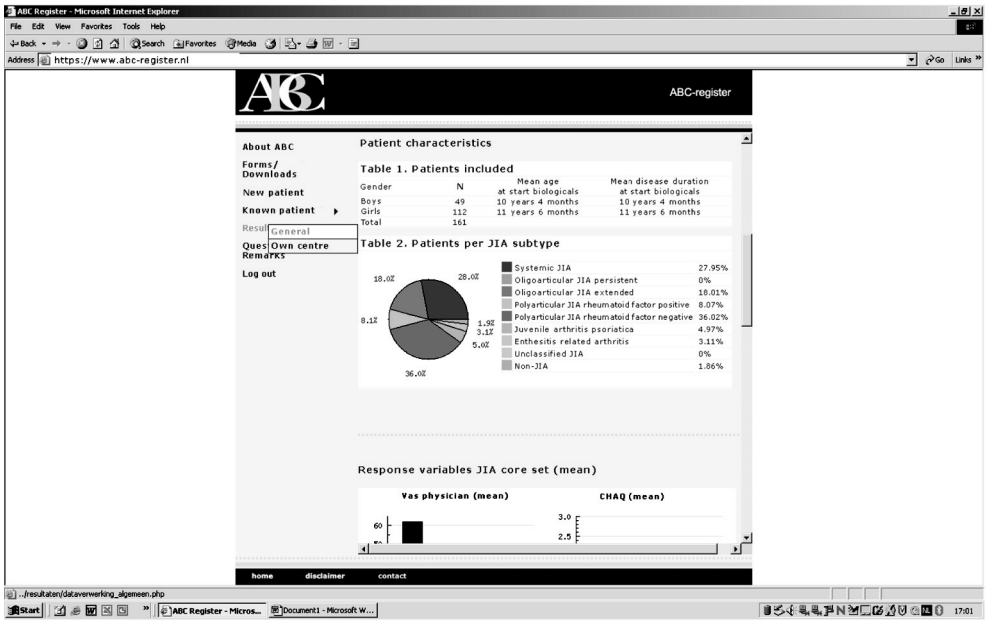

Figure 3.2: Screenshot 2 (translated into English for publication) (see page 227 for color figure).
Reports; an example of an interim report of the combined imported data from all the participating centres. This part shows the patients included by gender, the mean age and the mean disease duration at start of the biological (Table 1) and the percentages of JIA subtypes included (Table 2).

As an extra the user can download several forms, such as the Childhood Health Assessment Questionnaire score form, the joint score-form and the informed-consent form.[12]

User-friendliness of the design was tested by most users in a joined meeting addressing the practical use of the register. An example was given entering 'new patient' as well as 'follow-up' data. After this, the inexperienced users were asked to enter data while recording the time needed. Comments on user-friendliness were processed.

Data saving and retrieval

Data entered are saved automatically as the user goes to the next screen, herewith preventing the risk of data loss. Imported data are automatically checked for major erroneous and completeness at the end of each step. At the end of the data entry process, a summary is presented and the user has to confirm the correctness of data. The user is able to change the data up to a month. Thereafter, the imported data are checked on inconsistencies and potential missing values by the investigator and secured. If the user would like to make changes after the data are secured, this can only be done by contacting the investigator.

Safety of privacy and security

The change from paper CRFs to a web-based register was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam. Privacy and security measures were taken to comply with the requirements of the Dutch privacy law and the Dutch law on medical treatment. Data of patients were made anonymous before they are stored in a central database. All participating centres will sign a contract regarding their responsibility over the implemented data.

Extensive security tools have been implemented to protect the register against unauthorized use. These include, among others, individual logins and password for users and investigators. Users can only access patients form their own centre; investigators have access to all patients. When logged in incorrectly three times, the account will be blocked and the user has to contact the webmaster. The system also registers as to which user logs in and can link this to the imported data.

To reduce the risk of data loss due to browser or PC failure, data entered by the user are saved as each screen is completed. Facilities were made for backup of data for at least ten years. Anti-virus software is installed, and will be updated on a regular basis.

Security experts from Erasmus MC insured that all requirements concerning the protection of patient data were met. The security demands of the service provider and the web application were all checked. A security risk analysis was performed to anticipate possible safety risks.

Software

The following programs were used: Dreamweaver (for the design and realisation of the webpages), MySql (for the database) and PHP (for the link between database and webpages). The web server was installed and coordinated by external companies specialized in medical multimedia. The ABC logo and layout of the site was designed using QuarkXPress and Adobe Photoshop. The register internet domain is made available at www.abc-register.nl

RESULTS

The web-based register was first tested by the investigators with the data from all 41 study patients from the Erasmus MC Sophia Children's Hospital. After data entry several issues in usability were encountered and successfully adjusted. For instance, we discussed as to what to do with patients who discontinued a biological. We decided to keep these patient cases open for data entry as follow-up data of these cases are highly desired. To prevent confusion these patients would be marked with 'stop' in the overview unless they restart a biological. Other issues concerned time frame calculations to appoint follow-up data to fixed time points and minor adjustments in the layout to improve user-friendliness.

All imported data from the register could be automatically converted into an SPSS file. Since the original database (in which the data from the paper CRFs was imported) consisted of an SPSS file as well, data could be easily compared. Some errors were detected and correction of false couplings was needed and performed. Next, the investigators tested the ABC register with the data from all 161 included patients from nine different centres. In order to check if all information about the centre was given correctly and to verify if data from other centres were not accessible, we logged into the register using the specific password of a user of that centre.

User implications

The users were positive about the layout, readability and order in which data had to be entered. They all judged the amount of entered data as sufficient and saw no need in adding extra. The mean duration of data entry in the web-based register on a new patient was 4 min 33 s vs. 4 min 25 s on paper CRF. The follow-up assessment entry took an average of 2 min 22 s vs. 2 min 40 s on paper CRF. The users judged the time needed for data entry acceptable. No errors were found in the imported data.

At first all data regarding a specific patient had to be entered at once. This was judged as a disadvantage by the users as some data are not known immediately. Now the user is notified if data are missing, but may proceed data entry despite missing data. The investigator will contact the user if the data are still missing after 30 days.

A user suggested providing a paper overview of data needed for the web-based register as a reminder. We therefore designed a mouse pad with an overview of the data needed, an email address to be used for help and the website address of the register.

Safety tests

The inaccessibility to patient data for unauthorized visitors was tested when the Computer Emergency Response Team (CERT) tried to hack into the ABC register unsuccessfully. After multiple safety tests the CERT as well as the security officer and the officer for protection of personal information of the information department concluded that the web-based ABC register was safe to use as a data collection tool.

DISCUSSION

By developing a web-based register we have digitalized the CRF and achieved our aim to provide easy and rapid access to the database. As most scientific clinical studies use paper CRFs to collect data, such a web-based register can also be used for other type of studies, like clinical trials or cohort studies.[8-10] An advantage for the user is the possibility to check own data at any given moment and the general data of all participating centres combined. Continuous accurate output and reports will improve the collaboration between the centres and promote involvement.[8-10] The advantage for the investigator is the continuous access to

a complete, up-to-date, multicentre database. In addition, it saves the investigator time since data collection has been automated and visits to local centres are reduced.

The velocity and simplicity of data entry, has to stimulate the physician to use the register.[7,8] At the fixed follow-up moments for each patient, physicians will automatically be reminded through an email to update the patient data into the register.

Nevertheless, the register does request physicians to be alert and report side-effects, flares, therapy withdrawals and therapy changes, since automatic reminders are not possible for these situations. Connecting the register to the electronic medical records of each centre would improve completeness of the database and increase user-friendliness.[7] This is certainly a recommendation for the future.

A potential drawback of a web-based register is that it brings the risk of losing entered data or problems with data entry due to browser or PC failure. Therefore, it is essential to provide an excellent back-up system to prevent loss of data.

In addition, when the register is not designed properly it may lead to the production of misleading data.[8] For this reason, testing of the register by investigators and users is important to secure internal validity.

We expect that the use of web-based registers will greatly expand over the next decade and that many collaborative study groups will find it an efficient tool to collect data.

By reporting the process of developing a web-based register for biologicals in JIA (the ABC register) and the advantages of using such a register, we hope to have contributed to a new way of data collection for clinical research.

ACKNOWLEDGMENTS:

We thank: M. Belder and J. Vermond for their help in creating the website; J.W. Schoemaker, P. van Hoogdalem and the CERT team for making the web-based register safe and secure; and dr. N.M. Wulffraat for his involvement in the ABC project. The ABC project was funded by the Dutch Board of Health Insurances. Wyeth International financially supported (unconditionally) the development of the ABC-register.

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Chapter 4

Systematic monitoring of Juvenile Idiopathic Arthritis disease activity in daily practice

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Development of a digital Childhood Health Assessment Questionnaire for systematic monitoring of disease activity in daily practice

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ABSTRACT

Objective: To develop a reliable and user-friendly digital Childhood Health Assessment Questionnaire (CHAQ) to facilitate systematic monitoring of disease activity at the outpatient clinic in Juvenile Idiopathic Arthritis (JIA) patients.

Methods: The digital CHAQ was tested with patients who visited the outpatient paediatric rheumatology clinic of the Erasmus MC Sophia Children's Hospital. These patients completed in a randomized order the paper form and digital CHAQ while being observed. Validity was tested by comparing outcomes with the paper form CHAQ. User-friendliness was evaluated through a short questionnaire.

Results: A digital CHAQ was developed and revised several times according to our observations. Outcome is automatically calculated and can be printed. Fifty-one patients completed both the digital and paper form CHAQ. Correlation coefficient between both outcomes of the CHAQ Disability Index was 0.974. No statistically significantly differences in median outcome were found in Visual Analogue Scale (VAS) pain (25.6 mm vs. 25.9 mm) and VAS well-being (20.1 mm vs. 19.5 mm). Although the mean time (5.06 minutes) to complete the digital CHAQ was significantly longer than the mean time (3.75 minutes) to complete the paper form, the majority of patients (75%) preferred the digital version. User-friendliness received maximum positive score.

Conclusion: We developed a reliable and user-friendly digital CHAQ, which can be easily and systematically completed during routine clinic visits. Such digitalization of questionnaires can be applied in any field to make systematic monitoring of disease activity in daily practice possible.

INTRODUCTION

In adults with rheumatic diseases systematic monitoring of the disease activity in clinical practice has proven to lead to better treatment resulting in a lower disease activity.[1] Monitoring influence of disease activity by Health-Related Quality of Life (HRQoL) questionnaires provides valuable information about the impact of treatment.[2-4] However, in daily practice the use of HRQoL measurements seems to be limited.[2,4-6] Therefore, several studies in adults have been preformed to improve use of HRQoL questionnaires.[2,7-10] Until now no studies in children have been reported.

Juvenile Idiopathic Arthritis (JIA) is a chronic disease in children that can lead to functional, physical and psychosocial disabilities in everyday life. In order to evaluate disease activity during treatment, the JIA core set of response variables is used.[11,12] This score consists of the following response variables: physician's global evaluation of disease activity on a 100-mm Visual Analogue Scale (VAS), number of active and number of limited joints, erythrocyte sedimentation rate and the Childhood Health Assessment Questionnaire (CHAQ) including an evaluation of the child's pain and overall well-being by a VAS. The first four variables are routinely measured during each visit at our outpatient paediatric rheumatology clinic; however, the CHAQ is not.

The CHAQ measures disability and discomfort of JIA patients and has been cross-culturally adapted and validated also in The Netherlands.[13-15] Although the CHAQ was developed for either self- or proxy-reporting, in several Dutch children's hospitals it is mostly scored through interview by an experienced paediatric physiotherapist in more severe JIA patients or in patients who participate in a clinical study.[13,14] In order to achieve complete systematic monitoring of disease activity in all JIA patients, the CHAQ should be completed by every patient at every outpatient paediatric rheumatology clinic visit.[16]

The principal aim of this study was to develop a reliable and user-friendly digital CHAQ to complete systematically at the outpatient paediatric rheumatology clinic during routine visits. The outcome of this CHAQ should be calculated automatically and be available during the patient's visit.

METHODS

Development of a digital CHAQ

The validated Dutch version of the paper form CHAQ was used for this study.[15] It consists of 30 items in eight different domains covering most aspects of daily life: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. For each functional area there is at least one question relevant to children of all ages. Each item is scored from 0 to 3 (0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do; or not applicable e.g. because of the young age and therefore not calculated in score). If help or helping devices are used in a certain domain the minimum score is 2. For calculating the final score (CHAQ Disability Index, CHAQ_DI) the highest scores of every domain are summarised and divided by eight (eight domains). The presence of pain and the child's overall well-being is rated on a VAS (scale 0-100 mm with 0 being the best possible score). Answers should reflect the child's situation over the last week.

To develop the digital CHAQ, we first made a preliminary design in Microsoft PowerPoint software. The text was equal to the validated paper form.[15] However, we slightly changed the order of some items to optimize user-friendliness. The paper form evaluates the use of help or helping devices only twice; once after the first four domains and once after the last four domains. We decided to evaluate this directly after each domain. In this way, one domain is finished before starting the next one.

After we completed the design of the digital CHAQ, an external company specializing in medical multimedia converted this design into a computer program. Before testing the digital CHAQ in the clinical setting, professionals experienced with the paper form CHAQ and five patients tested a first version on a regular computer. Adjustments were made according to their remarks.

We developed a parent-version (CHAQ-PV) and a child-version (CHAQ-CV) with minor differences in language. No specific age was determined for children to complete the CHAQ-CV. In both versions we inserted drawings of Jip and Janneke© by Fiep Westendorp, which are well known in The Netherlands, to clarify each domain and make it more attractive for the children as well as their parents. As an example, several screens from the final design of the digital CHAQ-PV are shown in figure 4.1 A, B and C.

Use of the digital CHAQ

The physician's assistant fills in the patient's personal data, which remain visible at every page. The patient/parent continues and decides whether to complete the CHAQ-PV or the CHAQ-CV. Subsequent pages supply general instructions, similar to the instructions written on the validated paper version. Then all items are completed and finally the VAS pain and VAS well-being are scored by moving a bar across a horizontal line. Centrally, we placed above this line a smiley face changing facial expression from extremely happy at the left end to extremely sad at the right end.

To follow the process a summery of all domains is given at each page changing colour during completion (figure 4.1 A, B, C). Participants are able to return to previous pages to make changes when desired. The automatically calculated outcome shows the answers of each item as well as the final scores of the CHAQ_DI, VAS pain and VAS well-being. The outcome is printed and attached to the patient's file before the patient visits the physician (figure 4.2).

Safety and data savings

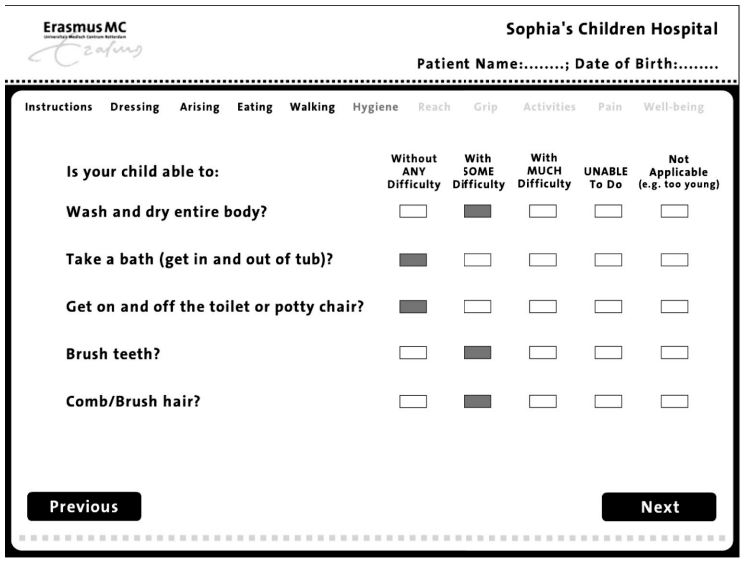
Security measures were applied. Before entering new data a password is asked. Data are saved on the hard disk. An overview of all participants is available after entering the password again. By clicking on the patient's name his/her questionnaire can be recalled, changes can be made and the outcome can be printed again. Prints are kept in the patient's paper file.

Testing the digital CHAQ

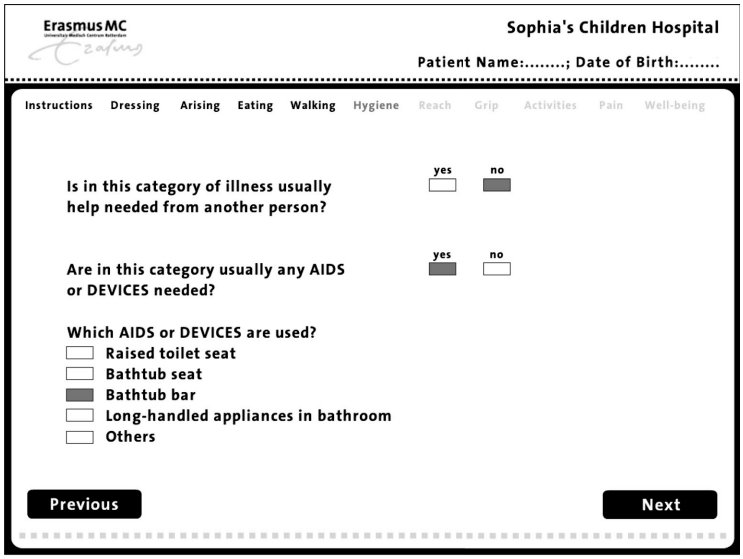
During one month we included all consecutive JIA patients visiting the outpatient paediatric rheumatology clinic of the Erasmus MC Sophia Children's Hospital. Participants with insufficient knowledge of the written Dutch language were excluded. Patients or parents were asked to complete both the paper form CHAQ and the digital CHAQ in a randomized order. They were observed during completion to see which problems they encountered and to record time needed. No further instructions were given.

We analyzed data using the Wilcoxon signed rank test, the Paired-Samples t-test or Independent-Samples t-test as appropriate. Correspondence of outcomes of the CHAQ_DI was analysed by linear regression with zero intercept. A p-value < 0.05 was regarded statistically significant. Analyses were performed using the SPSS statistical package, version 15.0.1 (Chicago, IL, USA).

Figure 4.1: Examples of screens of the digital CHAQ (translated in English for publication) (see page 228 and 229 for color figure). **Screenshot A; Domain 'Hygiene' is announced**



Screenshot B; The five items of the domain 'Hygiene' are completed



Screenshot C; The use of aids or devices in the domain 'Hygiene' is evaluated

We evaluated the layout of the digital CHAQ, its user-friendliness and the patient's preference with a short questionnaire. Comments and observations were used for revision.

The study was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam.

Figure 4.2; Example of the automatically printed outcome showing the results from the digital CHAQ from the Erasmus MC Sophia Children's Hospital (translated into English for publication)

Erasmus MC
University Medical Center Rotterdam

Test date:
Name:
Date of birth:
PID:

Page 1 of 2

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	Not applicable
1 DRESSING & GROOMING					
♦ Dress, incl. tying shoelaces and doing buttons	-	X	-	-	-
♦ Shampoo his/her hair	-	X	-	-	-
♦ Remove socks	X	-	-	-	-
♦ Cut fingernails	-	-	-	-	X
Help needed: no					
Aids or devices needed: no					
2 ARISING					
♦ Stand up from a low chair of floor	X	-	-	-	-
♦ Get in and out of bed or stand up in crib	X	-	-	-	-
Help needed: no					
Aids or devices needed: no					
3 EATING					
♦ Cut his/ her own meat	-	X	-	-	-
♦ Lift a cup or glass to mouth	X	-	-	-	-
♦ Open a new cereal box	-	X	-	-	-
Help needed: no					
Aids or devices needed: no					
4 WALKING					
♦ Walk outdoors on flat ground	X	-	-	-	-
♦ Climb up five steps	X	-	-	-	-
Help needed: no					
Aids or devices needed: no					
5 HYGIENE					
♦ Wash and dry entire body	-	X	-	-	-
♦ Take a tub bath (get in & out of tub)	X	-	-	-	-
♦ Get on and off the toilet or potty chair	X	-	-	-	-
♦ Brush teeth	-	X	-	-	-
♦ Comb/ Brush hair	-	X	-	-	-
Help needed: no					
Aids or devices needed: yes					
Aids or devices: Bathtub bar					

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	Not applicable
6 REACH					
♦ Reach and get down a heavy object such as a large game or books from just above his/ her head	-	-	X	-	-
♦ Bend down to pick up clothing or a piece of paper from the floor	X	-	-	-	-
♦ Pull a sweater over his/ her head	-	X	-	-	-
♦ Turn a neck to look back over shoulder	X	-	-	-	-
Help needed: no					
Aids or devices needed: no					
7 GRIP					
♦ Write or scribble with pen or pencil	-	X	-	-	-
♦ Open car doors	X	-	-	-	-
♦ Open jars which have been previously opened	-	X	-	-	-
♦ Turn faucets on and off	X	-	-	-	-
♦ Push open a doorknob	X	-	-	-	-
Help needed: no					
Aids or devices needed: no					
8 ACTIVITIES					
♦ Run errands and shop	X	-	-	-	-
♦ Get in and out of car or toy car or school bus	X	-	-	-	-
♦ Ride bike or tricycle	X	-	-	-	-
♦ Do household chores (e.g., wash dishes, take out trash, vacuuming, yard work, make bed, clean room)	-	X	-	-	-
♦ Run and play	-	X	-	-	-
Help needed: yes					
Aids or devices needed: no					

For check:
1 : 1
2 : 0
3 : 1
4 : 0
5 : 1
6 : 2
7 : 1
8 : 1

Sum of item scores: 7

Corrected sum of item scores: 9

Total score CHAQ: 1.125

VAS pain: 34

CHAQ well-being: 39

RESULTS

Testing the digital CHAQ

In a one-month period 54 patients with JIA visited our outpatient paediatric rheumatology clinic. Three of these patients were not included in our study; one patient because of insufficient knowledge of the written Dutch language and two patients because they did not agree to participation (because of lack of time and personal motives). Patient characteristics of the remaining 51 patients, as shown in table 4.1, are representative for the overall JIA population. The median age was 11.2 years [interquartile range (IQR) 8.1-15.0 years].

Half of the patients (26) started with the digital version and after that they completed the paper form version. The remaining 25 patients started with the paper form version and thereafter completed the digital version. Of all patients 33 (65%) completed the questionnaire by themselves; of whom the youngest was 9.7 years old.

During testing several difficulties were encountered. When children were too young to perform certain activities parents were likely to choose the option 'not possible' instead of 'not applicable', even though this is explained in the onscreen instructions. For clarification we added under the option 'not applicable' '(e.g. too young)'. Participants were likely to miss items during completion. Therefore we adjusted the restriction that all items of the page have to be fully completed before you can turn to the next one. To improve user-friendliness we enlarged the letters and buttons to facilitate completion.

Digital CHAQ versus paper form CHAQ

We found a clear correlation between the outcomes of the digital and the paper form CHAQ_DI (linear regression coefficient 0.974, $p < 0.001$). However, the median outcome of the paper form was 0.06 lower than the digital CHAQ respectively 0.66 (IQR 0.13-1.13) vs. 0.72 (IQR 0.00-1.25) ($p = 0.032$ by the Wilcoxon signed rank test). Also a clear correlation was found between paper and digital version on the VAS pain (linear regression coefficient 0.989, $p < 0.001$) and VAS well-being (linear regression coefficient 0.951, $p < 0.001$) No statistically significantly differences were found in median outcome between paper and digital version of the VAS pain respectively 25.6 mm (IQR 10.2-48.3) vs. 25.9 mm (IQR 10.7-51.0) ($p = 0.467$ by the Wilcoxon signed rank test) and VAS well-being respectively 20.1 mm (IQR 8.4-43.3) vs. 19.5 mm (IQR 7.9-34.0) ($p = 0.555$ by the Wilcoxon signed rank test).

Table 4.1: Patient and disease characteristics (N = 51)

Characteristics	N	(%)
Sex		
Male	15	(29.4)
Female	36	(70.6)
Median age in years (IQR)	11.2	(8.1-15.0)
Subtype JIA		
Systemic	7	(13.7)
Polyarticular rheumatoid factor positive	2	(3.9)
Polyarticular rheumatoid factor negative	15	(29.4)
Oligoarticular persistent	18	(35.3)
Oligoarticular extended	4	(7.8)
Enthesitis related arthritis	1	(2.0)
Juvenile arthritis psoriatica	4	(7.8)
Unclassified	0	(0)
Familiarity with CHAQ*		
Yes	18	(35.3)
No	33	(64.7)

IQR: interquartile range; JIA: Juvenile Idiopathic Arthritis; CHAQ: Childhood Health Assessment Questionnaire
*The patient or parents had completed the CHAQ at least one time before this study.

We explored whether the differences in outcome between the paper form and digital version were the same if children answered the questionnaires themselves (CHAQ-CV) or when parents did this (CHAQ-PV). The mean differences of the scores (deltas) of the CHAQ-CV and the CHAQ-PV were not statistically significantly different (delta CHAQ_DI $p = 0.568$, delta VAS pain $p = 0.784$ and delta VAS well-being $p = 0.276$ by the Independent-Samples t-test).

The mean time (5.06 minutes, SD = 1.91) to complete the digital CHAQ was significantly longer than the mean time (3.75 minutes, SD = 1.84) to complete the paper form ($p = 0.005$ by the Paired-Samples t-test). However, the majority (75%) of the patients preferred the digital version, 14% had no preference and 11% preferred the paper form. Layout and feasibility received a maximum median score of 5 (possible range 0-5). In addition, more interaction between parents and patients was observed during the completion of the digital CHAQ.

The mean time for completing the paper form was 3.72 minutes (SD = 1.40) in patients familiar with the CHAQ (n = 18) and 3.76 minutes (SD = 2.15) in the other patients. The mean time for completing the digital CHAQ was respectively 5.44 minutes (SD = 2.21) compared to 4.85 (SD = 1.77) minutes. No statistically significantly difference was found between the group who was familiar with the CHAQ and the group who completed the CHAQ for the first time (p = 0.194 for the paper form and p = 0.516 for the digital CHAQ by the Independent-Samples t-test).

DISCUSSION

We succeeded in our aim to develop a user-friendly digital CHAQ to be completed systematically at the outpatient paediatric rheumatology clinic. There is a clear correspondence between outcomes of this digital and the paper form CHAQ. We did find a lower outcome in the paper form CHAQ_DI, the absolute mean difference was 0.06 on a scale from 0 to 3. Since the total score of all domains is divided by eight (eight domains) to calculate the final score, the minimal change in outcome is 0.125, therefore, we do not consider this difference of 0.06 to be relevant. Participants recorded the use of help or helping devices in total 85 times in the digital CHAQ compared with 71 times in the paper form version, which might explain the difference in outcome. So in the digital form this information is gathered more accurately.

The majority of the patients and parents preferred the digital CHAQ although it took more time to complete. This is in accordance with results from studies in adults.[7,9,17] However, because in our study we dealt with paediatric patients and parents, we had to make the digital CHAQ appealing for children as well as adults. We succeeded in this goal since both patients and parents found the digital version easier to read because of the larger letters and it was more appealing due to the added colours and drawings. Although the drawings of Jip and Janneke are originally designed for children from age 2 to 8 years old, older children did not find the drawings childish. These drawings, which have existed since 1952, are cherished by people of all ages because they all grew up with their stories. For instance, recently a large Dutch department store has used Jip and Janneke drawings for teenage school supplies.

Parents of young children experienced more interaction with their child while completing the digital version, which was considered a big advantage. In the future, a touch-screen computer will be used to improve user-friendliness even further. Another option for the

future is making the digital CHAQ available online. This way, the patient or parent could already complete the CHAQ at home prior to the hospital visit.

A completed paper form questionnaire might contain missing values or multiple answers to one question. In our digital CHAQ the participant cannot continue unless all items of the page are completed and only one answer is accepted. Furthermore, four participants did not complete the two VASs on paper because they did not understand the question. The observer had to supply further instructions. Uncertainties were not observed during completion of the digital CHAQ.

Scoring the paper form CHAQ takes time and calculation errors can easily be made. The digital version calculates these scores automatically, which makes them more accurate and immediately available during the patient's visit. In the future, the digital CHAQ could be connected to the electronic medical records.

No significant time difference was found between patients familiar with the CHAQ and those who were not. However, the patients familiar with the CHAQ were previously interviewed on the CHAQ, which is considered very different from completing the digital or paper form version. We expect patients to complete the questionnaire faster when they have become more familiar with it.

There have been several studies in adults on the use of digital health status questionnaires; however our study is the first who reports experiences in a paediatric population.[7,8,10,17] Although only JIA patients were included in our study, the CHAQ can also be applied in children with other chronic musculoskeletal diseases.[13] More generic questionnaires could be used for systematic evaluation of other medical conditions. In general, digitalization of questionnaires can be applied in every field of clinical practice.

In our setting with the digital CHAQ, participants choose themselves between self-reporting or proxy-reporting. Parents can reliably report for their children.[14] A previous study showed fair to good agreement between self- and proxy-reporting regarding disability (CHAQ_DI) and well-being (VAS well-being) and only poor agreement for pain (VAS pain).[18] Therefore, in this study we did not determine an age limit for self-reporting. Besides, the questionnaire was completed most times by the patient and parents together.

It was unclear whether the fact that facial expression of the smiley face could be changed by moving the bar would influence the answer of the participants on the VAS. However, no significant differences in outcome between the digital and paper form VAS pain and VAS well-being were found.

Electronic patient files are more commonly used in hospitals. Digital questionnaires could be easily attached to these files. They can be completed while waiting for the physician. However, while implementing this digital CHAQ in daily practice, several things have to be considered. Participants with insufficient knowledge of the written Dutch language or with an impaired cognitive function still need more instructions or even help during completion, similar to the use of the paper form. All patients and parents have to be instructed that the questions relate to the child's situation over the last week and that limitations should only be registered in a domain if they are caused by the disease. In, addition, the option 'not applicable' should be well explained.

In conclusion, by developing a digital CHAQ we realized a systematic way to monitor disease activity in a paediatric population according to the recommendations for how to increase the use of HRQoL questionnaires.[2] The reliable and user-friendly digital CHAQ can be completed during routine visits at the outpatient clinic in only five minutes and the printed outcome (with automatically calculated scores) is available during the visit.

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Part 3

Effectiveness and Safety

Chapter 5

Long-term effectiveness and safety of etanercept in Juvenile Idiopathic Arthritis

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ABSTRACT

Objective: We undertook an observational study to obtain a complete overview of the long-term effectiveness and safety of etanercept in patients with different juvenile idiopathic arthritis (JIA) subtypes.

Methods: At baseline we collected patient and disease characteristics of all Dutch patients with JIA who started treatment with etanercept. Disease activity was evaluated (at start of the study, after 3 months and then yearly) according to the JIA core set of the American College of Rheumatology paediatric definition for 30, 50 and 70% improvement (ACR Pedi 30, 50 and 70). Use of etanercept and concomitant drugs was monitored. Adverse events were recorded.

Results: We included 146 patients with JIA with a median follow-up of 2.5 years per patient (range 0.3–7.3). JIA subtypes represented: 27% systemic, 8% polyarticular rheumatoid factor positive, 38% polyarticular rheumatoid factor negative, 19% oligoarticular extended, 3% enthesitis-related and 5% psoriatica. Most patients (77%) met the criteria of the ACR Pedi 30 in the first 3 months of treatment. For the majority of patients this improvement was sustained; 53 (36%) of all patients met the remission criteria. No other second-line agents were needed in 43 patients. Although patients with systemic JIA responded initially less to etanercept therapy than patients from other subtypes, those who did respond showed equal effectiveness in the long term. Serious adverse events rate was low (0.029 per patient year).

Conclusions: Etanercept is effective and safe in JIA, even for a large proportion of the patients with systemic JIA. The greatest improvement occurred in the first 3 months of treatment, and was sustained for a long time in most patients (up to 75 months).

INTRODUCTION

In recent years, tumour necrosis factor alpha (TNF-α) blocking medication has become a treatment option in Juvenile Idiopathic Arthritis (JIA).[1,2] Etanercept is currently the most frequently prescribed TNF-α blocking medicine in polyarticular-course JIA. It binds to TNF-α and TNF-β (lymphotoxin α) preventing it from interacting with the receptors on the cell surfaces.[3,4]

Lovell et al. first reported on the clinical benefit and safety of etanercept in 69 patients with polyarticular-course JIA in a clinical controlled trial.[5] These patients were thereafter followed in an open-label extension study, and efficacy and safety of etanercept were showed over a period of four years. However, the disease course was not described in detail for all the different JIA subtypes.[6,7] Several other open-label studies produced good initial efficacy of etanercept, however, they either involved small patient groups or they took no account of the difference in onset subtype.[8-12] Horneff et al. were the first to describe a registry on etanercept in JIA, including 322 patients; 84% were included in the evaluation of efficacy, with a maximum follow-up of four years.[13]

To obtain a complete overview of the long-term efficacy and safety of etanercept in relation to the different onset subtypes, we performed a long-term study in all JIA patients who started treatment with etanercept in the Netherlands.

PATIENTS AND METHODS

Subjects

In the Netherlands patients with JIA are eligible for treatment with etanercept if the condition has a polyarticular-course, and if the response to the maximum or maximum tolerated dose of methotrexate (MTX) proved to be insufficient. When the TNF-α blocking medication was included in the Medications Reimbursement System by the Ministry of Health, Welfare and Sport, a central evaluation board was installed to evaluate each patient. All patients younger than 18 years in the Netherlands with JIA of different subtypes, in whom etanercept use was granted by the central evaluation board from 1999 until 2006, were included in our national survey. The database from the central evaluation board, that had to approve etanercept

treatment for each individual patient in the Netherlands, was used to insure completeness. The study was financed by the Board of Health Insurances.

Study design

This prospective ongoing multicentre, observational study is coordinated by Erasmus MC Sophia Children's Hospital. The protocol was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam. Written informed consent was obtained, and the study was conducted in accordance with the Declaration of Helsinki.

The following data were collected at baseline: patient and disease characteristics, including gender, age at onset of JIA, age at start of etanercept use, disease duration, subtype of JIA, medical history, previous medication and concomitant drugs at start etanercept, starting dose of etanercept and disease activity. Every patient was evaluated by the central evaluation board at start and after the first three months of treatment. Follow-up data (disease activity, observed adverse events, etanercept dose and concomitant drug use) were collected at three months and every year thereafter. There were no limitations in the use of concomitant drugs. If etanercept was withdrawn, the reason for withdrawal was reported.

The outcome measures used to assess disease activity consisted of the following JIA core set of six response variables: 1) overall assessment of the disease activity by the physician through the visual analogue scale (VAS) (range 0-100 mm); 2) childhood health assessment questionnaire (CHAQ) (range 0-3) by the patient; 3) overall assessment of well-being by the patient through the VAS (range 0-100 mm); 4) number of active joints (joints with swelling not caused by deformity, or joints with limited motion, and with pain, tenderness, or both); 5) number of joints with limited motion; and 6) a laboratory marker of inflammation, erythrocyte sedimentation rate (ESR).[14]

Efficacy analysis

Efficacy was assessed using the American College of Rheumatology Paediatric 30, 50 and 70 criteria (ACR Pedi 30, 50 and 70).[14] This definition states that there should be at least 30% improvement (50% or 70% dependent on the score) from baseline in three of any six variables in the JIA core set with no more than one of the remaining variables worsening by > 30%. Patients in whom etanercept was stopped within the first three months of treatment were marked as initial non-responders. Patients were marked as secondary non-responders if they discontinued etanercept because of a disease flare as judged by the treating physician.

When patients discontinued etanercept in the event of remission the treatment was considered to be successful. For evaluation purposes we used the criteria by Wallace et al. for remission on medication, which had to be met for more than six months and are defined as: no active arthritis, no fever, rash, serositis or generalized lymphadenopathy attributable to JIA, no active uveitis, normal ESR and a physician's overall assessment of disease activity that indicated no disease activity.[15] We defined ESR values under 16 mm/hour as normal. We stated that a physician's overall assessment score below the 20 mm (instead of 0 mm) on the VAS indicated no disease activity.

Safety analysis

All medical important adverse events (AEs) and all serious adverse events (SAEs; defined as events that were life threatening or fatal, or resulted in a disability, handicap, congenital anomaly or birth defect, or required inpatient hospitalization) were reported by the treating physicians on a continuous base. In addition, the investigators frequently searched for AEs in all the patient files in order to ensure the completeness of data. Flaring of JIA, as judged by the treating physician, was not recorded as an AE, but as measurement for response to etanercept. We calculated the patient-year rate of SAEs (for the period that etanercept was used and 30 days after discontinuation) on the base of duration of exposure to etanercept.

Statistical analysis

Baseline characteristics were listed and summarized. Response variables were evaluated according to the ACR Pedi 30, 50 and 70. Missing values (5.1% of the JIA core set response variables was missing) were imputated using the aregImpute function by F. Harrell.[16] Only follow-up data with less then 50% of the response variables missing were used for imputation. When appropriate the chi-square test and the Mann-Whitney test were used to compare the responses (using level of significance $p < 0.05$). Adherence to therapy was estimated with Kaplan-Meier plots and differences were defined by the log rank test (significance $p < 0.05$).

Analyses were performed using the SPSS for Windows package, version 14.0.1, except for imputation of missing values, which was performed with the R package, version 2.4.1.

RESULTS

Patient and disease characteristics

Table 1 shows the patient and disease characteristics and previous JIA therapy of the 146 patients included in the study. All patients were treated in one of the nine centres with experienced paediatric rheumatologists (range from 5 to 41 patients per centre). Most patients received etanercept in the usual dose of 0.4 mg/kg twice weekly; in 28 patients etanercept was initiated or changed in the double dose of 0.8 mg/kg once weekly. Median duration of etanercept therapy was 1.7 years (range 0.1 to 6.8 years). Total follow-up time was 436.1 patient-years (median of 2.5 years per patient, range 0.3 to 7.3 years). Four patients had a history of uveitis; one of these patients still had an active uveitis at start of etanercept.

Clinical outcome

Figure 1 shows the flowchart outlining follow-up of all patients. The number of patients who discontinued etanercept for reasons of non-responding, adverse event or complete remission was noted per follow-up period. In the subsequent follow-up periods, these patients were omitted from the analysis.

The improvement from baseline and the results of the response variables are shown in table 2. The table contains data from patients who responded to etanercept treatment. In general, there was a major improvement for all JIA subtypes in all variables after three months of treatment. However, systemic JIA patients improved significantly less than other JIA subtypes on the ACR Pedi 30, 50 and 70 scores ($p < 0.01$ for all three scores) in the first three months of therapy.

During the study period, 53 of all 146 patients met the remission criteria (19 patients had a physician's overall assessment score between 0 and 20 mm instead of the strict 0 mm). The percentages of all included patients per subtype, who met those remission criteria were: 38% systemic JIA (sJIA), 32% oligoarticular JIA extended (oJIA ext), 38% polyarticular rheumatoid-factor negative JIA (pJIA RF-), 36% polyarticular rheumatoid-factor positive JIA (pJIA RF+), 50% JIA psoriatica (PsJIA).

Drug withdrawal and survival analysis

Figure 2 shows the Kaplan-Meier analysis of the proportion of patients that continued etanercept on grounds of efficacy; sJIA patients are shown separately from other JIA subtypes. This survival analysis indicates that etanercept is more likely to be withdrawn in patients with sJIA on grounds of inefficacy than in patients with other JIA subtypes ($p < 0.001$ by log rank test).

Table 5.1: Patient and disease characteristics at start etanercept (N=146)

Characteristics	N	(%)
Median age (years)	11.2	
Sex		
Female	101	(69)
Male	45	(31)
Onset subtype JIA		
Systemic	39	(27)
Polyarticular rheumatoid factor positive	11	(8)
Polyarticular rheumatoid factor negative	55	(38)
Oligoarticular extended	28	(19)
Ethesitis related arthritis	5	(3)
Juvenile arthritis psoriatica	8	(5)
Unclassified	0	(0)
Median disease duration JIA (years)	4.1	
History of drug use before start etanercept		
NSAIDs	141	(97)
Glucocorticosteroids systemic	90	(62)
Glucocorticosteroids intra-articular	60	(41)
MTX	146	(100)
Other DMARDS	74	(51)
Use of other concomitant drugs at start etanercept		
NSAIDs	122	(84)
Glucocorticoids	67	(46)
MTX	113	(77)
Other DMARDS	13	(9)

JIA, Juvenile Idiopathic Arthritis; NSAID, Non-Steroid Anti-Inflammatory Drug; DMARD, Disease Modifying Anti-Rheumatic Drug; MTX, Methotrexate

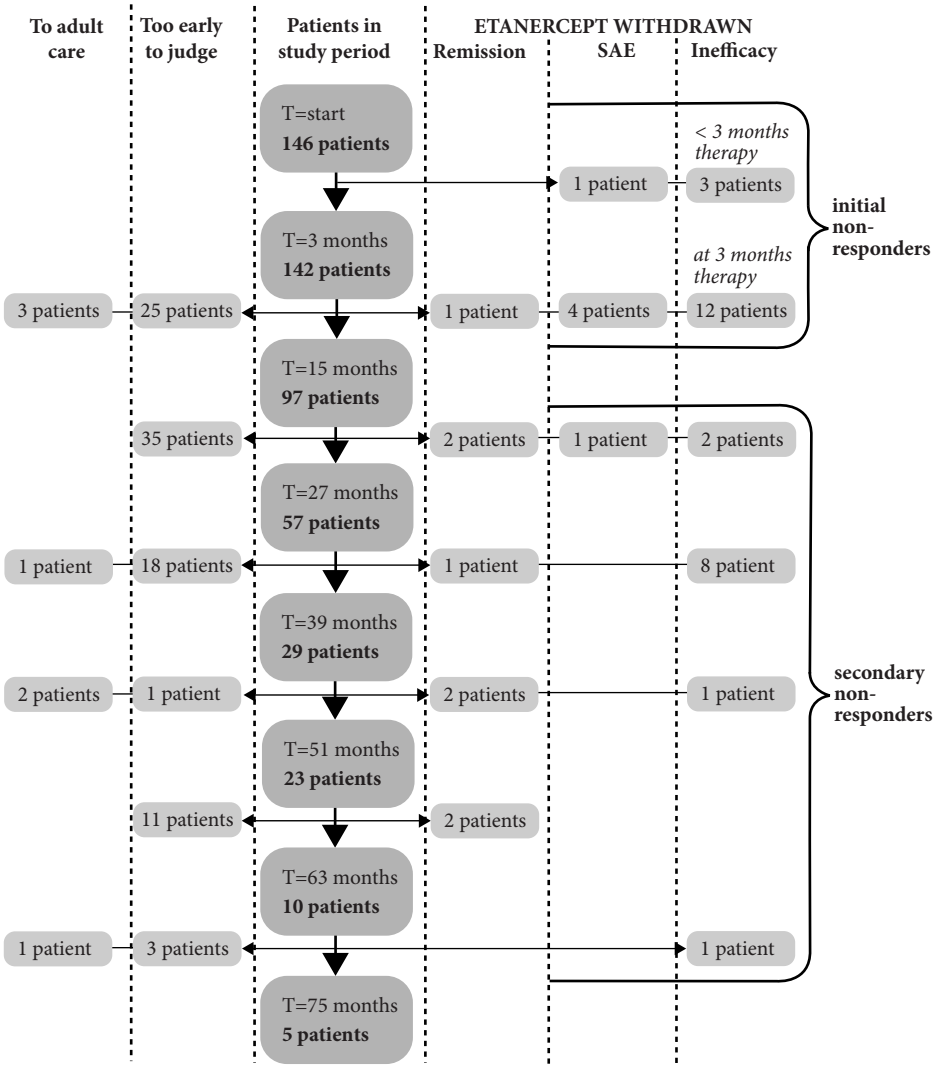

Figure 5.1: Flowchart of patients in study using etanercept

Etanercept therapy was discontinued in 20 initial non-responders and in 13 secondary non-responders (22 sJIA, 1 pJIA RF+, 6 pJIA RF-, 4 oJIA ext). Disease duration at start of etanercept in non-responders compared to responders was neither in total patient group ($p = 0.56$) nor in the systemic patient group ($p = 0.38$) statistically significantly different. In

nine (41%) of the non-responding sJIA patients flaring of systemic features was observed after discontinuation of etanercept.

Of the 33 patients who discontinued etanercept 17 patients did not switch to another biological. Of these patients 88% received NSAIDs, 76% received MTX, 65% received systemic glucocorticoids and 18% were given intra-articular glucocorticoids injections after discontinuation of etanercept. The other 16 patients (14 sJIA patients and 2 oJIA ext patients) switched to another biological (6 infliximab, 4 adalimumab and 6 anakinra). Eight did not respond to the other biological either (5 infliximab, 2 adalimumab and 1 anakinra) One started a third biological (anakinra after etanercept and adalimumab), however again no improvement was seen.

All patients used at least one concomitant drug at the start of etanercept treatment (table 1). During the first 15 months of etanercept treatment, NSAIDs were discontinued in 37% of all patients who used it at start and glucocorticosteroids in 67%. Although 22% of all patients using MTX at start discontinued its use during treatment with etanercept, MTX had to be restarted in 8% of those patients. All other DMARDs were discontinued. In total 43 patients successfully discontinued all other second-line agents besides etanercept.

During the first 15 months follow-up time 18 patients received one or more intra-articular glucocorticoids injections.

Safety

During 312 observed patient-years of etanercept use, 65 AEs were reported as shown in table 3. The majority of AEs occurred during the first 15 months of treatment (49 during 133 patient-years). Additional second-line agents were used by 68% of the patients with non-infectious AEs, 77% of the patients with infectious AEs and 89% of the patients experiencing a SAE. Occurrence of AEs was not statistically significant different ($p = 0.25$) between the different JIA subtypes.

Serious adverse events (SAEs) occurred in nine patients; the SAE rate was 0.029 per patient-year. Etanercept was definitively discontinued in six cases due to SAEs. Three patients continued etanercept despite having a SAE: a patient after colitis caused by E. coli, a patient who experienced convulsions, since a history of epileptic attacks had been reported before the use of etanercept and an other patient who developed sarcoidosis. The two patients with an inflammatory bowel disease as well as the two patients with sarcoidosis had no signs of these diseases before the start of etanercept.

Table 5.2: Improvements on the JIA core set of six response variables (A) and evaluation by ACR Pedi score (B)

	Start		3 months		15 months		27 months		39 months		51 months		63 months		75 months	
A. Median per core set response variable (25%-75%)																
VAS physician	68	(53-78)	15	(8-29)	10	(2-23)	10	(2-20)	11	(4-32)	5	(0-10)	6	(0-14)	10	(5-35)
CHAQ (0-3)	2.0	(1.2-2.4)	1.0	(0.4-1.8)	0.4	(0-1.0)	0.4	(0-1.0)	0.8	(0.2-1.4)	0.3	(0-0.9)	0.6	(0.1-1.1)	0.9	(0.5-1.6)
VAS well-being	54	(27-76)	10	(2-40)	5	(0-26)	8	(0-27)	6	(0-45)	10	(0-36)	9	(0-59)	30	(6-58)
active joints #	12	(7-22)	2	(0-6)	1	(0-3)	0	(0-6)	1	(0-4)	0	(0-2)	0	(0-2)	1	(0-5)
limited joints #	9	(6-14)	5	(2-9)	2	(1-6)	0	(0-6)	4	(2-9)	3	(2-5)	3	(1-5)	3	(2-7)
ESR (mm/h)	27	(15-46)	10	(5-20)	8	(5-17)	4	(1-7)	11	(5-32)	8	(4-16)	7	(4-15)	16	(5-33)
	Start		**3 months**		**15 months**		**27 months**		**39 months**		**51 months**		**63 months**		**75 months**	
B. Patients per JIA subtype (%)																
Total population	*N=146*		*N=142*		*N=97*		*N=57*		*N=29*		*N=23*		*N=10*		*N=5*	
ACR30			112		90		50		21		21		7		3	
ACR50			95		88		46		19		21		7		3	
ACR70			72		74		40		15		17		6		2	
Remission					35		27		9		11		5		1	
Systemic JIA	*N=39*		*N=37*		*N=24*		*N=16*		*N=9*		*N=8*		*N=4*		*N=0*	
ACR30			22		21		14		6		8		4			
ACR50			16		20		13		6		8		4			
ACR70			10		16		10		5		7		4			
Remission					9		8		5		7		4			
Polyarticular JIA RF+	*N=11*		*N=11*		*N=9*		*N=5*		*N=4*		*N=4*		*N=3*		*N=3*	
ACR30			9		8		3		3		3		1		2	
ACR50			8		8		3		3		3		1		2	
ACR70			6		7		2		2		2		1		1	
Remission					3		1		0		1		1		1	

Table 5.2 Continued

	Start	3 months	15 months	27 months	39 months	51 months	63 months	75 months
B. Patients per JIA subtype (%)								
Polyarticular JIA RF-	N=55	*N=53*	*N=36*	*N=24*	*N=10*	*N=8*	*N=2*	*N=1*
ACR30		48	33	21	8	7	1	0
ACR50		42	33	18	6	7	1	0
ACR70		33	28	17	5	6	1	0
Remission			14	12	2	3	0	0
Oligoarticular JIA	*N=28*	*N=28*	*N=18*	*N=9*	*N=3*	*N=2*	*N=1*	*N=1*
ACR30		22	18	9	1	2	1	1
ACR50		20	17	9	1	2	1	1
ACR70		16	15	8	1	1	0	0
Remission			6	5	1	0	0	0
ERA	*N=5*	*N=5*	*N=4*	*N=2*	*N=2*	*N=1*	*N=0*	*N=0*
ACR30		4	4	2	2	1		
ACR50		4	4	2	2	1		
ACR70		4	3	2	1	1		
Remission			0	0	0	0		
JIA Psoriatica	*N=8*	*N=8*	*N=6*	*N=1*	*N=1*	*N=0*	*N=0*	*N=0*
ACR30		7	6	1	1			
ACR50		5	6	1	1			
ACR70		3	5	1	1			
Remission			3	1	1			

ACR30, 50, 70, American College of Rheumatology Pedi score 30, 50, 70 [14]; Remission, criteria of remission by Wallace et al. on medication [15]; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale (0-100); CHAQ, children's health assessment questionnaire sJIA, systemic JIA; pJIA RF +, polyarticular rheumatoid factor positive JIA; pJIA RF-, polyarticular rheumatoid factor negative JIA; oJIA ext, oligoarticular extended JIA; ERA, enthesitis-related arthritis; PsJIA, juvenile arthritis psoriatica

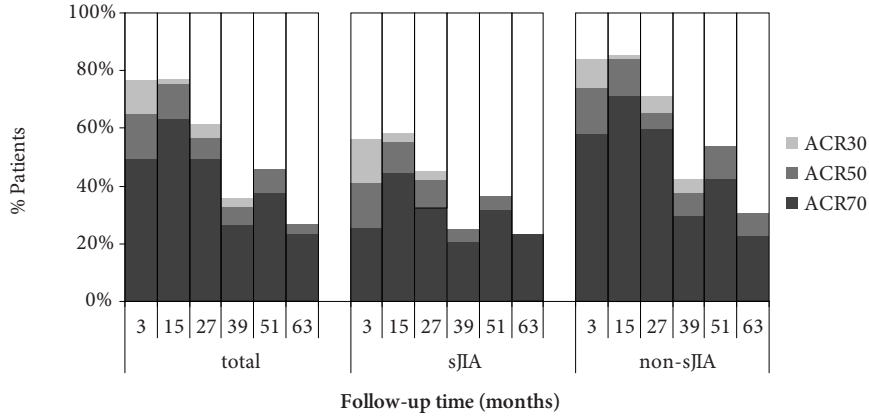

Figure 5.2: Improvement according to the ACR Pedi score in percentages of patients based on the intention-to-treat-modus. Shown in this figures are the percentages patients (who could have reached that fixed follow-up moment after start etanercept treatment) that met the criteria for the ACR Pedi 30, 50 or 70 (all patients, sJIA, non-sJIA).

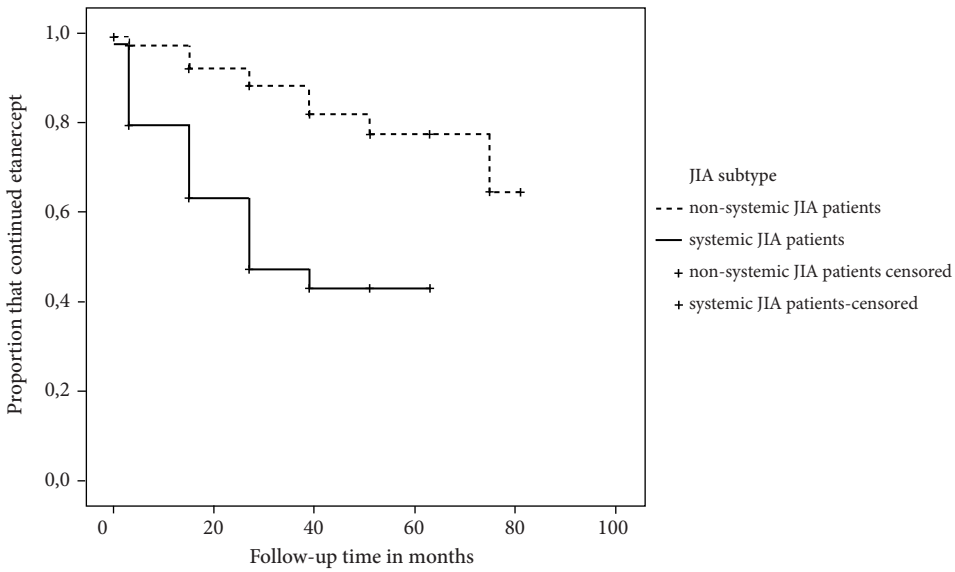

Figure 5.3: Kaplan-Meier survival analysis of etanercept use

Table 5.3: Reported adverse events (AEs) and serious adverse events (SAEs) during etanercept treatment

	Total
Non-infectious	39
nausea	8
injection-site reactions	7
headache	6
fatigue	5
concentration disorder	3
chronic cough	2
hair loss	2
rash	2
vomiting	1
abdominal pain	1
weight loss	1
osteoporosis	1
Infectious	17
fever of unknown origin	7
otitis	2
upper respiratory tract infection	2
gastro-intestinal infection	2
lymphadenopathy	1
infection ear lobe	1
Herpes infection	1
Epstein Barr virus-infection	1
Serious adverse events	9
gastro-intestinal infection	3
sarcoidosis	2
collitis ulcerosa	1
Crohn's disease	1
epileptic insult	1
uro-sepsis (E. coli and Enterococ)	1

None of the patients included in our study showed signs of demyelinization, or malignancies and no new cases of uveitis were reported during the course of the study and none of the patients died on etanercept therapy.

Three systemic JIA patients, who did not respond to etanercept died after multiple immunosuppressive treatments that also failed. One patient who discontinued treatment with etanercept and started treatment with infliximab developed tuberculosis under treatment with infliximab, and died.[17] None of the other patients in our study developed tuberculosis. One patient died of a suspected macrophage activation syndrome and another patient died of a suspected sepsis masked by the use of immunosuppressive drugs. All three patients were initial non-responders and had not used etanercept for at least eight months when they died.

DISCUSSION

In this paper the results are presented from our prospective open-label study in which we consecutively included all JIA patients in the Netherlands who used etanercept. The data from this Dutch register proved, in a real-life setting with an unselected and complete patient population, the initial but also the sustained effectiveness of etanercept in JIA up to 75 months. This is a promising result considering that the patients in the study had not previously responded to other second-line agents, including the maximum (tolerated) dose of MTX. The greatest improvement took place in the first three months. It confirms findings from previous studies, indicating that rapid improvements can be made with etanercept.[5,10,13] Furthermore, we showed that generally a steady state of improvement was reached after 15 months (table 5.2). In this steady state small disturbances sometimes occurred in some patients. However, considering that some patients have severe disease flaring even though they were previously in remission, we have to conclude that etanercept cannot always completely suppress the activity in all JIA patients.

Although our study has the longest follow-up period reported in the literature until now, previous studies already report on the long-term follow-up of etanercept in JIA. Lovell et al. showed sustained benefit and safety of etanercept in JIA in a four years open-label extension study. However, this study group was relatively small (58 patients) and the patients already proved to be initially responsive to etanercept before entering the extension study.[5-7] The German registry on etanercept in JIA presented by Horneff et al. concerned a large study

population including 322 patients. Of these patients 270 (84%) were included in the efficacy analysis, which may have led to selection bias. They also did not describe the patient and disease characteristics as explicitly as we did.[13]

Our analysis of the outcomes of the JIA core set of six response variables shows that the variable limited joints made the least improvement during follow-up. As Lovell et al. suggested in their study, this is not a quick response variable, and therefore not a good marker for short-term studies.[5]

In our study we found that early in treatment effectiveness appeared to be depended on the JIA subtype; in the first three months of treatment more patients with sJIA were unresponsive or less responsive to etanercept than those with other subtypes. Surprisingly, after 15 months of follow-up sJIA patients discontinued etanercept treatment about as frequent as patients from other subtypes. The sJIA patients who responded to etanercept showed the same improvement on the ACR Pedi score after a prolonged time and 38% of all sJIA patients included even reached remission on medication.

Previous to our study several other studies have also reported lower rate of responsiveness of sJIA patients to etanercept. Stated as possible reasons were the severity of disease and other factors such as IL-1 and IL-6 which might play a larger role in sJIA patients than in other subtypes.[9,18-20] However, in our study a great part of the sJIA patients was responsive to etanercept. We therefore conclude that it is reasonable to accept etanercept as the first choice in treatment of sJIA patients as long as no new treatments are available. Although in the literature different responses to anakinra in JIA patients are described, it has proved to be effective in some sJIA patients.[9,21,22] In our study five out of seven sJIA patients, who were unresponsive to etanercept, did respond to anakinra. Therefore, at the moment we suggest anakinra to be the next best choice of treatment for those sJIA patients who do not respond to etanercept, which in most cases can be concluded after three months of treatment.

Although etanercept does not induce remission in all patients, it seems to suppress disease activity in patients with refractory JIA. For instance, a great part of the sJIA patients (41%) who discontinued etanercept therapy due to persistent active arthritis developed fever and other systemic features. This suggests that etanercept did have some effect on the systemic disease activity.

Our study shows that physicians generally have the same therapy strategies in patients based on the response. One is to be cautious in changing treatment in patients who respond well to etanercept. In these patients physicians often reduce concomitant medication but act

with great caution regarding etanercept treatment, leading to continuation for many years for patients in complete remission. Until now no studies on how or when to stop etanercept in JIA patients in remission have been published.

The other strategy applies to the patients in whom disease activity fails to decline on etanercept, physicians are likely to treat these patients more aggressive and raise the dose and concomitant medication. If this fails etanercept is stopped and other therapy options are considered.

Some of the patients in this study received etanercept in the double dose of 0.8 mg/kg once weekly instead of the usual dose of 0.4 mg/kg twice weekly. Although there are no reports on controlled clinical trials investigating the double weekly dose in JIA patients, data from our study, as well as data from a clinical study by Kuemmerle et al. show no differences in effectiveness or safety compared to the usual dose.[23,24]

In accordance with previous studies on the safety of etanercept our long-term follow-up study reports a very low SAE-rate and few AEs.[5-10,25] None of the patients developed tuberculosis during etanercept treatment. This is consistent with other studies, which state that the incidence of tuberculosis is lower during etanercept treatment than during infliximab therapy.[26,27] However, two patients developed another granulomatous disease: sarcoidosis. To our knowledge, these are the first cases of sarcoidosis during etanercept therapy yet to be reported. Two patients developed a chronic inflammatory bowel disease (IBD) during etanercept therapy; colitis ulcerosa and Crohn's disease. Although several others cases of new onset IBD during etanercept use were reported, anti-TNF-alpha therapy (mostly infliximab but also etanercept) is described in the literature as a registered treatment of IBD.[10,13,28-32] This is contradictive and the mechanism behind it is still unknown. More research is required in this field.

It has to be taken into account that this was an observational study; only the clinically relevant AEs were reported by the physicians. This might have led to some underreporting compared to controlled clinical trials.

In conclusion, while this study confirms earlier findings that etanercept is effective and safe in JIA, it also shows that initial effectiveness varies in the subtypes of JIA. Overall sJIA patients improve significantly less in the first three months of therapy. However, those sJIA patients who do respond to etanercept therapy show levels of improvement comparable to those of patients with other JIA subtypes.

Although some unexpected SAEs occurred, etanercept was safe in JIA.

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Chapter 6

Health-Related Quality of Life during the use of etanercept in Juvenile Idiopathic Arthritis

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Major improvements in Health-Related Quality of Life during the use of etanercept in patients with refractory Juvenile Idiopathic Arthritis

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ABSTRACT

Objective: To evaluate changes in Health-Related Quality of Life (HRQoL) in patients with refractory Juvenile Idiopathic Arthritis (JIA) while treated with etanercept.

Methods: We included 53 JIA patients from seven Dutch centers. HRQoL was measured in these patients by the Childhood Health Assessment Questionnaire (CHAQ), Child Health Questionnaire (CHQ) and Health Utilities Index mark 3 (HUI3) at start and after 3, 15 and 27 months of treatment. At the same time points the following JIA disease activity variables were collected; physician's global assessment through the Visual Analogue Scale (VAS), number of active and limited joints and erythrocyte sedimentation rate. Statistical method Linear Mixed Models was used to assess outcomes over time.

Results: During etanercept therapy HRQoL improved dramatically on both disease specific and generic HRQoL outcomes. Significant improvements were shown after three months and these improvements continued at least up to 27 months of treatment.The disease specific CHAQ, including the VAS pain and VAS well-being showed a significant improvement on all domains. The generic health-profile measure CHQ improved on all the health concepts except for "family cohesion". The generic preference-based HUI3 showed significant improvement on the more specific domains "pain", "ambulatory", and "dexterity". In accordance also disease activity variables improved significantly over time.

Conclusion: This study shows that HRQoL of patients with refractory JIA can substantially be improved by the use of etanercept on all aspects impaired by JIA. Information on HRQoL is crucial to understand the complete impact of etanercept treatment on JIA patients and their families.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most common cause of chronic arthritis in childhood.[1,2] It frequently results in physical disabilities and chronic pain influencing daily life.[3,4] Since its introduction in 1999 etanercept has become an important treatment for patients with refractory JIA.[5-10] It binds to TNF-α and TNF-β (lymphotoxin-α) preventing it from interacting with the receptors on the cell surfaces.[11,12] In recent years several studies have shown an impressive decline of disease activity expressed by the JIA core set of response variables (which is seen as the golden standard to evaluate disease activity in JIA patients) during the treatment with etanercept.[8,9,13-18] On the other side, concerns have been expressed about possible serious adverse events on the long-term, such as severe infections, sarcoidosis, inflammatory bowel disease and especially malignancies.[8,9, 4,19,20] Little is known about the changes in Health-Related Quality of Life (HRQoL) in these patients, and no long-term prospective studies have been reported.[21]

HRQoL can be defined as the physical, emotional and social aspects of the much broader concept quality of life, influenced by an individual's disease and/or treatment.[22] Therefore HRQoL is an important outcome measure in understanding the total impact of a chronic illness and the treatment.[23,24]

The objective of this study was to describe changes in HRQoL during etanercept therapy in patients with refractory JIA.

PATIENTS AND METHODS

Patients and data collection

In The Netherlands JIA patients are eligible for treatment with etanercept if the disease has a polyarticular-course and the response to the maximum (tolerated) dose of methotrexate (MTX) was not sufficient. All Dutch JIA patients, younger than 18 years, treated with etanercept are included in the national Arthritis and Biologicals in Children (ABC) register to evaluate long-term effectiveness and safety of etanercept and other biologic agents.[9] This prospective, ongoing, multi-centre observational study is coordinated by the ErasmusMC Sophia Children's Hospital.

For all included patients data on patient and disease characteristics are collected in the ABC-register, including gender, date of birth, date of JIA onset, JIA subtype, medical history, previous medication and data on the use of etanercept such as dose, frequency, use of concomitant drugs and (serious) adverse events (AE). Also disease activity is evaluated and entered into the register at start of treatment, after 3 months, 15 months and every year thereafter. The disease activity response variables are: overall assessment of disease activity by the doctor through the Visual Analogue Scale (VAS) (range 0-100 mm); number of active joints (joints with swelling not caused by deformity, or joints with limited motion, and with pain, tenderness, or both); number of joints with limited rage of motion; and a laboratory marker of inflammation, erythrocyte sedimentation rate (ESR).[15] Also the Childhood Health Assessment Questionnaire (CHAQ) including two Visual Analogue Scales (VAS) for pain and well-being is recorded systematically in the register as disease activity variables.[15]

For the complete evaluation of the HRQoL we prospectively collected additional data from the patients in the register from 2003 until 2006. Seven of the nine Dutch pediatric rheumatology centers agreed to participate in this add-on study in the ABC-project. We added the Child Health Questionnaire (CHQ), a generic health profile measure, and the Health Utilities Index Mark 3 (HUI3), a preference-based measure questionnaire in order to provide a complete overview of the impact of etanercept treatment on HRQoL.[22,25-29] Eligible patients of all ages and JIA subtypes were asked to complete all HRQoL questionnaires at the start and after 3, 15 and 27 months of treatment.

The protocol was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam and local Medical Ethical Committee approval was given in every participating center. Written informed consent was obtained, and the study was conducted in accordance with the Declaration of Helsinki. The study was financed by the Board of Health Insurances from 2003 until 2006.

Health-related Quality of Life (HRQoL) instruments

Health status is an overview of a person's physical, psychological and social well-being. Functional status is an evaluation of the effect of a disease on the patient's ability to carry out activitities of daily living. HRQoL instruments are used in the clinical domain to measure both and include some aspect of the patient's own perception of the effect of a disease or treatment on his or her life.[24] For this study we used one disease specific measure of functional status, a generic health-profile instrument and a preference-based measure to fully evaluate HRQoL in these patients. The Dutch versions of all three questionnaires were validated.[22,29,30]

Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ including VAS for pain and well-being is considered the golden standard in pediatric rheumatology to evaluate the disease specific HRQoL.[15,22,31] This 30-item disease specific instrument measures disability and discomfort in children with JIA and other chronic musculoskeletal diseases.[24,31,32] The CHAQ disability index (CHAQ DI) is divided in eight different domains (dressing, arising, eating, walking, hygiene, reach, grip and activities) and is scored on a scale from 0 to 3 with 0 being the best possible score. The need for help of others or the use of aids or devices is taken into account and adjusted in the score.[33] In addition, the patient's pain and overall well-being is rated on a VAS from 0-100 mm with 0 as the best score. The Dutch version of the CHAQ was completed by patient or parent.[22]

Child Health Questionnaire (CHQ)

The CHQ is a generic health-profile measure which measures the physical and psychosocial well-being of children.[22,33] We applied the Dutch proxy version (CHQ-PF50) containing 50 items.[22] Answers are scored in 13 different health concepts: physical functioning (PF); role functioning: emotional/behavioral limitations (REB), role functioning: physical limitations (RP); bodily pain/discomfort (BP); general behavior perception (BE); mental health (MH); self-esteem (SE); general health perceptions (GH); change in health (CH); emotional impact on the parent (PE); impact on the parent's personal time (PT); limitations on family activities (FA) and family cohesion (FC). Concepts are rated on a scale from 0 to 100 with a higher score indicating a better health. All but three (CH, FA, FC) of these concepts are used for calculating two summary scores: the Physical summary Score (PhS) and the Psychosocial summary Score (PsS). Summary scores are transformed so that the mean is 50 and the standard deviation (SD) is 10.

Health Utilities Index Mark 3 (HUI3)

The HUI3 is a preference-based HRQoL measure that includes a classification system that indicates the level of impairment in eight domains (attributes) based on information retrieved by a 15-item parent questionnaire. These eight single-attributes in the HUI3 are vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, with each five or six levels representing the range of functioning from not (1) to severely impaired (5 or 6). We applied the single- and multi-attribute utility formulas suggested by Feeny et al. for estimating single- and multi-attribute utilities.[34] The latter is scored on a scale from 0 (dead) to 1 (perfect

health). In our study we used the proxy assessment since children are considered to be unable to value health states.[29]

Statistical analysis

All descriptives and frequencies including means, medians, standard errors and interquartile range (IQR) were calculated using statistical software SPSS 15.0.1. (SPSS Inc., Chicago Illinois, USA).

We tested if any significant changes were found comparing outcomes of HRQoL questionnaires and disease activity response variables over time using Linear Mixed Models to account for the correlations between the repeated measurements. We inserted disease duration at start of etanercept as a continuous covariance and onset JIA subtype (systemic and non-systemic JIA) as categorical covariance for all models. Intercept was set as random variable, time of questionnaire assessment, disease duration and JIA subtype as fixed variable. Compound symmetry was defined as covariance structure. We used a level of significance of $p < 0.05$.

RESULTS

Patient and disease characteristics

During the study period 71 JIA patients from seven different Dutch centers specialized in pediatric rheumatology were eligible to receive the HRQoL questionnaires. Of these patients 53 completed the three questionnaires during treatment with etanercept (75% response rate). In total we collected 453 questionnaires. The median age at start of etanercept was 11.9 years (IQR 8.1-14.9) with median disease duration of 3.0 years (IQR 1.6-5.1). The patient and disease characteristics (table 6.1) are representative for the 146 patients that were included in the ABC-register at the end of 2006.[9] No significant differences between groups were found (using respectively the two-sample-t-test and chi-square test) in disease duration before start of etanercept ($p = 0.13$) or JIA subtype being systemic or non-systemic ($p = 0.97$).

Etanercept was given in the dose of 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly.[35,36] History of anti-rheumatic drug use and concomitant drug use at start of etanercept are shown in table 6.1. All patients used at least one concomitant drug at the start of etanercept treatment (table 6.1). During the first 27 months of etanercept treatment, NSAIDs were discontinued

in 47%, glucocorticoids in 75%, and MTX in 26% of all patients using the concomitant drug at start of etanercept. All other DMARDs were discontinued. This all resulted in a total of 19 patients on mono-therapy etanercept. During the first 27 months therapy 9 patients received one or more intra-articular glucocorticoids injections.

Table 6.1: Patient and disease characteristics at start etanercept (N = 53)

Characteristics	N	(%)
Median age (years) at start ETN	11.9	
Sex		
Male	20	(38)
Female	33	(62)
Onset subtype JIA		
Systemic	14	(26)
Polyarticular rheumatoid factor positive	5	(9)
Polyarticular rheumatoid factor negative	18	(34)
Oligoarticular extended	11	(21)
Enthesitis related arthritis	2	(4)
Juvenile arthritis psoriatica	3	(6)
Median disease duration JIA (years) at start ETN	3.0	
History of anti-rheumatic drug use before start etanercept		
NSAID	53	(100)
Glucocorticoids systemic	33	(62)
Glucocorticoids local injection	24	(45)
MTX	53	(100)
Other DMARD	28	(53)
Concomitant drug use at start of etanercept		
NSAID	49	(92)
Glucocorticoids systemic	24	(45)
MTX	42	(79)
Other DMARD	5	(9)

ETN: etanercept; JIA: Juvenile Idiopathic Arthritis; NSAID: Non-Steroid Anti-inflammatory Drug; MTX: Methotrexate; DMARD: Disease Modifying Anti-Rheumatic Drug

Changes in HRQoL and disease activity

The outcomes of the disease activity response variables as well as the outcomes of the HRQoL questionnaires are shown in table 6.2.

The disease activity variables "VAS physician", "number of active joints", "number of limited joints" and ESR all improved statistically significant over time ($p < 0.001$).

Improvement of outcomes in the disease specific questionnaire during treatment (figure 6.1) lead to significantly different scores over time for the CHAQ DI ($p < 0.001$) as well as the VAS pain ($p < 0.001$) and the VAS well-being ($p < 0.001$) (table 6.2).

Outcomes of the 13 health concepts of the CHQ are shown in table 6.2 and figure 6.2 as well. During treatment we found a significant improvement ($p < 0.05$) in all but two of the health concepts (GH and FC). The scores of the CHQ domains PF, REB, RP, BP, GH and PE were very low at the start of treatment compared to those of healthy children.[22,30] Consequently also the summary scores of the CHQ at treatment start are very low; however both scores show a great improvement in outcome during treatment. The PhS started 2.5 SD under the score of healthy children but improves to almost minus 1 SD. The PsS was at start minus 0.5 SD; this score improves during treatment up till it reaches the same level as in healthy children. These changes in the summary scores (figure 6.2) were significant (respectively $p = 0.005$ and $p = 0.004$).

The single-attribute utility functions of all eight domains of the HUI3 are given in table 6.2 and figure 6.3.

Statistically significant changes were seen in domains "ambulatory" ($p = 0.02$), "dexterity" ($p = 0.02$) and "pain" ($p < 0.001$). The domains "vision", "hearing" and "speech" were normal from start of therapy and remained normal during etanercept use. The domain "emotion" was close to normal and did not improve over time. The baseline score (0.51) of the multi-attribute utility function was poor; during etanercept treatment it showed a significant improvement in outcome over time ($p = 0.001$, figure 6.3).

During the study period four (three systemic and one polyarticular rheumatoid factor positive JIA) patients discontinued etanercept because of inefficacy after a median use of 14.3 months (IQR 3.3-26.7), two were initial non-responders (they discontinued etanercept after 3 months of treatment due to inefficacy). Eight patients had an AE (AE rate 0.08 per patient year; four injection-site reactions, two concentration disorders, one upper respiratory tract infection and one nausea), however they did not discontinue etanercept use. One patient had a serious adverse event (SAE rate 0.010 per patient year), an epileptic insult, but continued

etanercept use as there was a history of epileptic insults before the start of etanercept therapy. All patients continued to fill in the HRQoL questionnaires after experiencing the (S)AE.

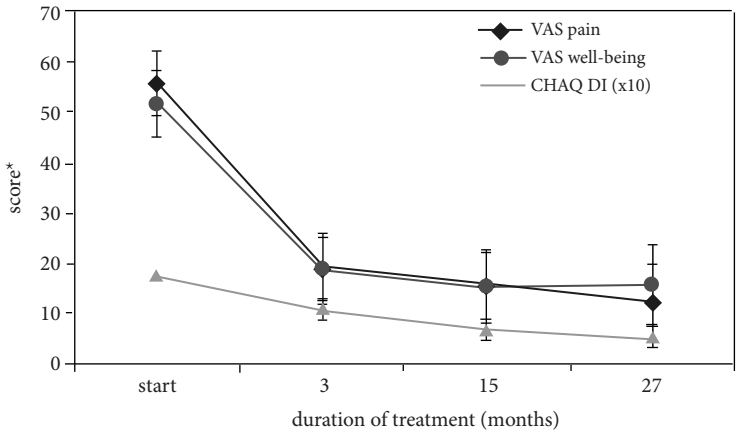

Figure 6.1: Childhood Health Assessment Questionnaire (CHAQ) (see page 230 for color figure)**;** Changes in mean outcomes during treatment with etanercept of the CHAQ DI, VAS pain and VAS well-being within 95% confidence limits (+/- 1.96*standard error of the mean).
CHAQ DI (x10): Childhood Health Assessment Questionnaire Disability Index score (range 0-3) multiplied by ten; VAS: Visual Analogue Scale (range 0-100)
*Change over time: CHAQ DI $p < 0.001$, VAS pain $p < 0.001$, VAS well-being $p < 0.001$

Table 6.2: Disease activity and health-related quality of life assessment in 53 JIA patients during treatment with etanercept

Parameters	Start	3 months	15 months	27 months		Healthy children*
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	p-Value	Mean ± SE
JIA disease activity response variables						
VAS physician (0-100mm)	66.0 ± 2.5	16.7 ± 2.5	14.6 ± 2.7	11.9 ± 3.0	<0.001	
Number of active joints	16.8 ± 1.0	4.47 ± 1.0	3.10 ± 1.0	2.34 ± 1.2	<0.001	
Number of limited joints	11.4 ± 0.8	5.93 ± 0.8	3.51 ± 0.8	3.13 ± 0.9	<0.001	
ESR (mm/h)	26.7 ± 2.0	12.2 ± 2.0	12.1 ± 2.1	11.3 ± 2.5	<0.001	
CHAQ						
CHAQ Disability Index (0-3)	1.73 ± 0.1	1.07 ± 0.1	0.69 ± 0.1	0.54 ± 0.1	<0.001	0.2 ± 0.4
VAS pain (0-100mm)	55.6 ± 3.3	19.3 ± 3.3	15.8 ± 3.5	12.4 ± 3.9	<0.001	0.0 ± 0.2
VAS well-being (0-100mm)	51.6 ± 3.3	18.5 ± 3.3	15.3 ± 3.6	15.8 ± 4.0	<0.001	0.0 ± 0.1
CHQ (0-100)						
Physical summary score (PhS)	24.7 ± 2.6	32.7 ± 3.1	31.5 ± 3.7	39.6 ± 4.7	0.005	55.6 ± 1.9
Psychosocial summary score (PsS)	45.1 ± 1.4	49.4 ± 1.7	50.7 ± 2.1	53.6 ± 2.7	0.004	53.1 ± 6.7
Physical functioning (PF)	51.1 ± 4.3	61.6 ± 5.0	67.5 ± 5.8	82.2 ± 7.2	<0.001	99.2 ± 3.2
Role functioning: emotional/ behavior (REB)	60.8 ± 5.0	72.2 ± 6.0	74.0 ± 7.2	87.9 ± 9.2	0.02	98.0 ± 10.5
Role functioning: physical (RP)	49.6 ± 5.1	69.3 ± 6.1	62.7 ± 7.2	72.3 ± 9.2	0.007	99.8 ± 1.9
Bodily pain discomfort (BP)	41.9 ± 4.3	52.7 ± 5.4	57.1 ± 6.8	72.1 ± 8.6	0.009	92.8 ± 12.5
Behavior (BE)	73.3 ± 2.0	77.2 ± 2.3	79.9 ± 2.6	83.1 ± 3.3	0.007	79.4 ± 13.9
Mental health (MH)	69.9 ± 2.3	75.2 ± 2.9	76.3 ± 3.5	83.7 ± 4.5	0.03	81.4 ± 13.1
Self-esteem (SE)	63.4 ± 2.1	69.8 ± 2.6	72.7 ± 3.1	71.4 ± 4.1	0.02	82.3 ± 13.2

Table 6.2: Continued

Parameters	Start	3 months	15 months	27 months		Healthy children*
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	p-Value	Mean ± SE
CHQ (0-100)						
General health (GH)	43.2 ± 3.0	46.7 ± 3.6	43.9 ± 4.4	50.5 ± 5.5	0.53	82.6 ± 16.1
Change in health (CH)	47.0 ± 5.4	67.3 ± 6.7	73.0 ± 8.3	76.1 ± 10.5	0.004	53.3 ± 11.9
Emotional impact on parent (PE)	47.7 ± 3.5	63.7 ± 4.2	65.6 ± 5.1	74.3 ± 6.4	<0.001	89.2 ± 16.6
Impact on parent's personal time (PT)	65.6 ± 3.5	79.3 ± 4.3	79.6 ± 5.4	94.8 ± 7.3	0.001	94.8 ± 11.8
Family activities (FA)	67.5 ± 3.4	73.7 ± 4.0	76.9 ± 4.7	85.0 ± 6.0	0.02	88.1 ± 12.9
Family cohesion (FC)	70.1 ± 2.7	70.9 ± 3.2	73.8 ± 3.9	68.6 ± 4.9	0.77	74.3 ± 20.5
HUI3 (0-1)						
Single-attribute utility functions						
Vision	0.99 ± 0.00	0.99 ± 0.00	0.99 ± 0.00	0.99 ± 0.00	n/a	
Hearing	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	n/a	
Speech	0.99 ± 0.00	0.99 ± 0.01	0.99 ± 0.01	1.00 ± 0.01	0.38	
Ambulatory	0.92 ± 0.02	0.96 ± 0.02	0.96 ± 0.02	0.96 ± 0.02	0.02	
Dexterity	0.92 ± 0.01	0.95 ± 0.02	0.97 ± 0.02	0.97 ± 0.02	0.02	
Emotions	0.96 ± 0.01	0.95 ± 0.01	0.97 ± 0.02	0.97 ± 0.02	0.34	
Cognition	0.96 ± 0.02	0.96 ± 0.02	0.97 ± 0.02	0.98 ± 0.02	0.47	
Pain	0.80 ± 0.02	0.89 ± 0.02	0.88 ± 0.03	0.93 ± 0.03	<0.001	
Multi-attribute utility function	0.51 ± 0.04	0.64 ± 0.05	0.70 ± 0.06	0.77 ± 0.08	0.001	

SE: Standard error of the mean; CHAQ: Childhood Health Assessment Questionnaire; CHQ: Child Health Questionnaire; HUI3: Health Utilities Index Mark 3; n/a: not applicable (since the scores remained unchanged over time)

*Reference values from healthy Dutch children[22]

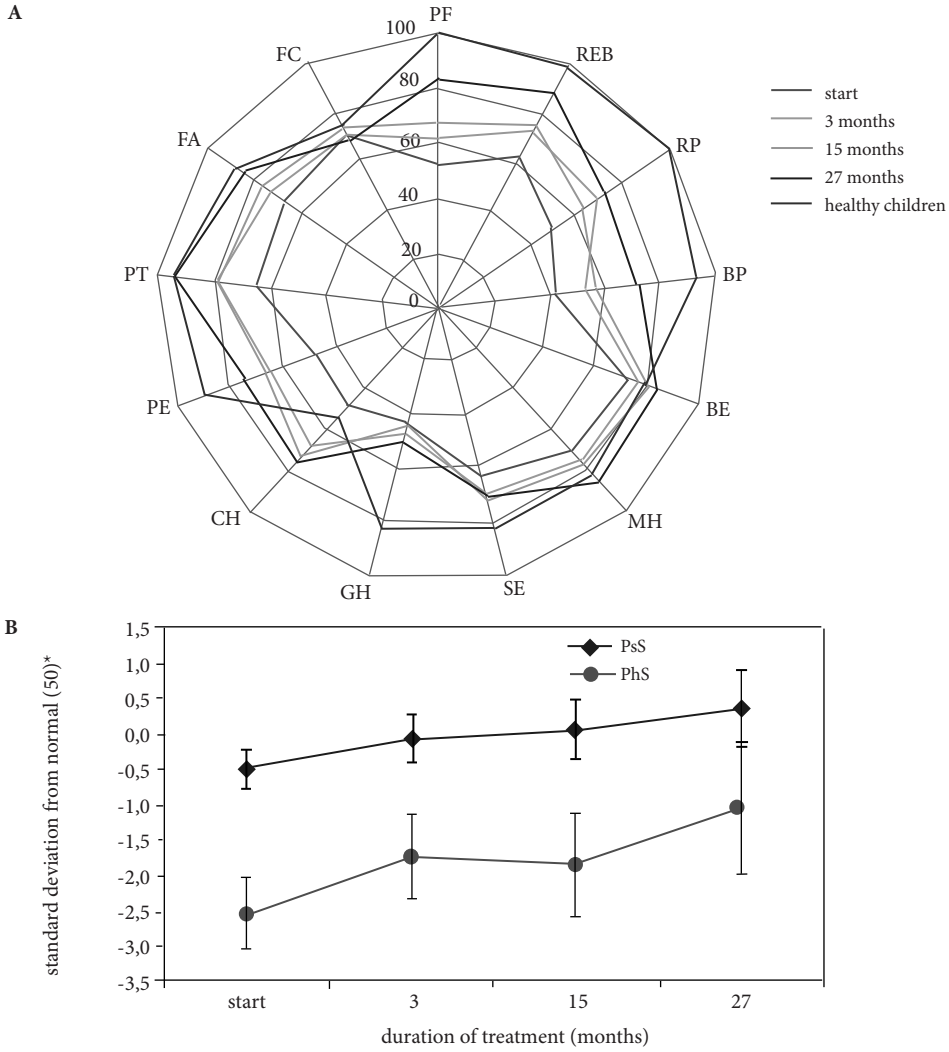

Figure 6.2 A and B: Child Health Questionnaire (CHQ) (see page 231 for color figure)**.**
Changes in mean outcomes during treatment with etanercept in all health concepts (A) compared to the outcomes in healthy children.[22] Changes in the PhS and PsS summary scores (B) within 95% confidence limits (+/- 1.96*standard error of the mean). The PhS and PsS summary scores are expressed in standard deviation from the normal mean value of 50.[22] PF: Physical functioning; REB: role functioning: emotional/behavioural limitations, RP: role functioning: physical limitations; BP: bodily pain/discomfort; BE: general behaviour perception; MH: mental health; SE: self-esteem; GH: general health perceptions; CH: change in health; PE: emotional impact on the parent; PT: impact on the parent's personal time; FA: limitations on family activities and FC: family cohesion. PhS: Physical summary Scale; PsS: Psychosocial summary Scale. *Change over time: PhS p = 0.005, PsS p = 0.004

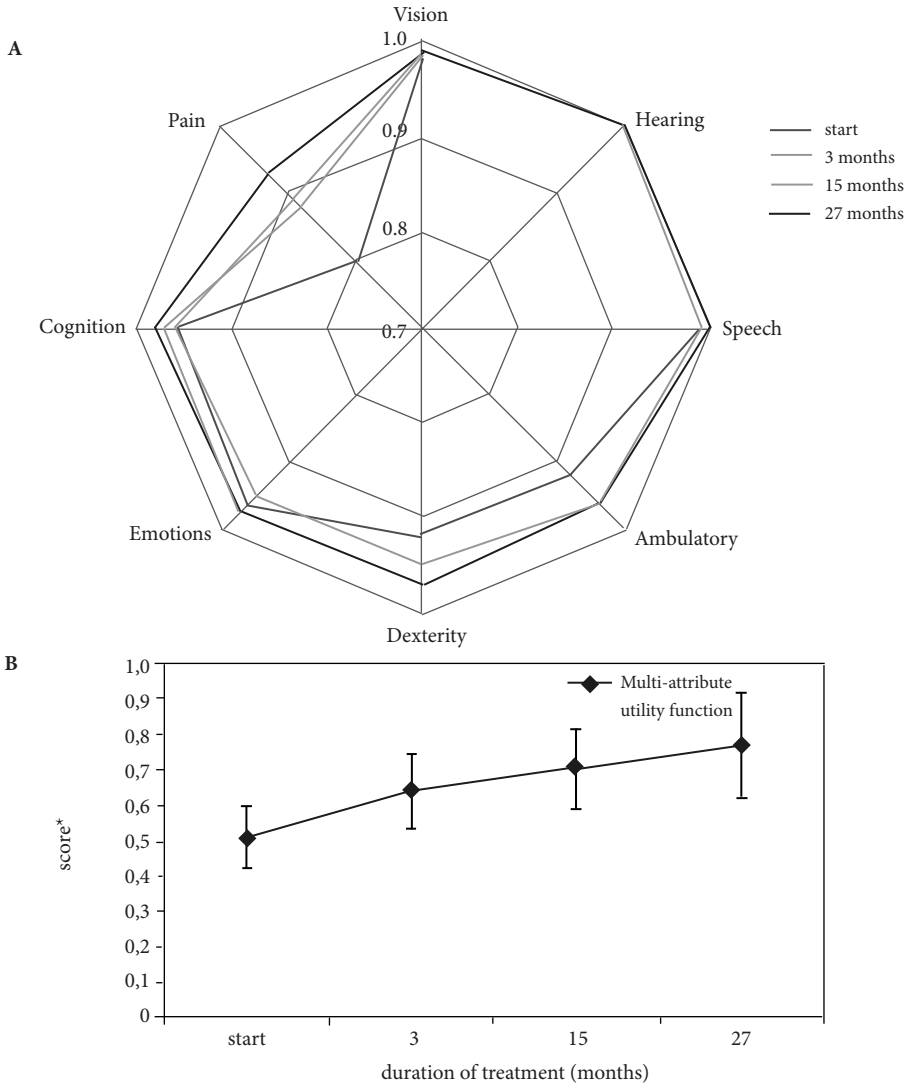

Figure 6.3 A and B: Health Utilities Index Mark 3 (HUI3) (see page 232 for color figure)**.**
Changes during treatment with etanercept in the mean single (A) and multi-attribute utility (B) function scores (range 0-1) on a death-health scale within 95% confidence limits (+/- 1.96*standard error of the mean). *Change over time: multi-attribute utility function p=0.001

DISCUSSION

This is the first prospective long-term study on HRQoL changes in JIA patients during etanercept treatment. The results are impressive as they show major improvement of HRQoL in refractory JIA patients during a period of 27 months of etanercept use. This is highly relevant considering that these patients had a high disease activity score and very poor HRQoL at start of etanercept and previously had not responded to other second-line agents including MTX.

Previous studies have shown the efficacy of etanercept in declining disease activity in Juvenile Idiopathic Arthritis (JIA) on the short-term and long-term.[7-9,14,16,37] However, it is important to also describe a treatment effect on HRQoL since children with a chronic illness such as JIA have a higher risk for behavior and emotional disorders.[38-40] We described the treatment effect of etanercept in children with a severe form of JIA, which causes pain, discomfort and deformity of joints. It is of great value to know for these children if a new treatment is likely to be successful in all aspects of health improvement.

The disease activity dramatically declines after three months of etanercept use and thereafter this improvement in health sustains (table 6.2). This course is the same in the outcomes of disease specific CHAQ and the VAS pain and well-being. These improvements continue over the following 24 months of treatment, although the VAS well-being appears similar at 15 and 27 months.

The scores of most of the CHQ domains are dramatically low at the start of treatment compared to those of healthy children.[22,30] These findings are comparable with the scores of JIA patients who started treatment with MTX and seem typical for JIA patient groups with severe disease activity.[41] However, during etanercept treatment these extremely low HRQoL levels greatly improve, sometimes even to the same level as in healthy children.[22,30] This is reflected in the PsS score, which means that in spite of the observation that JIA patients treated with etanercept still have some physical impairments, their overall psychosocial functioning improves to a score that is comparable to the general population. In addition, it is very reassuring that we did not only find an increasing improvement of the PhS after 3 months and 15 months of treatment, but even an additional strong improvement after 27 months. These findings indicate that improvements in physical health can still occur after prolonged treatment with etanercept, which is in line with the observation of an ongoing decrease in the number of active and limited joints over time (table 6.2).

Of all domains in the CHQ only "family cohesion" (FC) and "general health" (GH) do not statistically significantly improve. The finding that JIA has little impact on family cohesion is already reported in several other studies.[41,42] We suppose that the weekly injections with etanercept might be a reason why patients do not see themselves as healthy as their peers even though there is no or little disease activity, which is also reflected in the VAS well-being not improving further after 15 months of treatment.

The multi-attribute utility function of the HUI3 shows an impressive improvement over time. The poor baseline score (0.51) again indicates the serious impairments in health these JIA patients experience before the start of etanercept treatment. We did not expect to find domains such as "hearing" and "speech" to improve much during treatment, since these are not likely to be effected by JIA and the initial scores were close to a maximum score of 1. Domains like ambulatory, dexterity and pain, which are directly impaired by active JIA, reflected a positive change during etanercept therapy. However, the domain "emotion" did not improve as much as expected. Possibly this HUI3 domain is not sensitive enough to detect changes in emotions in JIA patients as relevant improvement in scales related to emotions are clearly seen in the CHQ score.

We compared the 53 patients in this add-on study with the initial 146 patients in the ABC-register to preclude selection bias.[9] No major differences in patient and disease characteristics between the subgroup and the total group from the register were found. In particular no significant differences were found on the severity of disease based on disease duration before start of etanercept and JIA subtype. Although AE and SAE occurrence slightly differs from the data of all the 146 patients from the ABC-register, findings are in line with safety data from other studies.[8,9,13,14,21] The subgroup of 53 patients contained less initial non-responders then the total group from the register. However, since the objective of our study was to report changes in HRQoL of JIA patients during long-term use of etanercept this will not effect the interpretation of the results. We did not specify HRQoL for the different JIA subtypes, since the groups were too small. Nevertheless, we did correct for JIA subtype in the analysis.

Although the total of 53 JIA patients seems small, this is a considerable number of patients in pediatric rheumatology. The long-term follow-up period and the use of three different questionnaires in combination with the high response rate make this study unique. Moreover, the preference based HUI3 was never used before in pediatric rheumatology, yet it is of great importance in determining HRQoL and is used a lot in other fields of pediatric research.[29,30]

Several other studies have reported on the improvement of the disease specific CHAQ during etanercept treatment, however not all studies have evaluated the VAS pain score.[7,8,14,15,21,25,32,37] This is an important measurement since pain together with disability are the most important determinants of physical and psychosocial well-being.[27,38,43,44] Moreover, no other prospective study has taken the generic CHQ and HUI3 into account although these have been validated for (rheumatic) pediatric patients.[22,29,30] In Rheumatoid Arthritis in adults the Health Assessment Questionnaire (HAQ) has become the primary measure of physical function, accompanied by the use of generic measures such as the HUI3 to assess HRQoL.[26] It is suggested that although joint counts and laboratory values are important parameters of disease improvement, in JIA HRQoL tools will become the ultimate indicators of measuring true treatment success.[25,45] The extremely low values at start of treatment and the major improvements in the complete HRQoL assessment demonstrated in our study are important to understand the complete impact of a treatment and balance the pros and cons. Therefore it is advisable to include disease specific and generic HRQoL assessments when evaluating the effectiveness of medication in JIA patients.[24,46]

In conclusion, our manuscript describes clinical relevant findings in the treatment of children with refractory JIA. Our findings are promising as they show great improvement on all domains of HRQoL impaired by JIA during the use of etanercept indicating that these previously severely ill children gain great benefits from this treatment. These improvements even further increase with continued etanercept therapy. The information on the HRQoL is an important additive on the information from the disease activity score presented in previous studies and is crucial to understand the complete impact of etanercept treatment on JIA patients and their families.

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Chapter 7

An analysis of the costs and treatment success of etanercept in Juvenile Idiopathic Arthritis

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An analysis of the costs and treatment success of etanercept in Juvenile Idiopathic Arthritis

ABSTRACT

Objective: To analyze and report the costs and effects of etanercept therapy in patients with Juvenile Idiopathic Arthritis (JIA).

Methods: Forty-nine JIA patients were evaluated by means of the JIA core set at start of etanercept, and after 3, 15 and 27 months of therapy. At the same time points parents of the patients were asked to complete the Health Utility Index mark 3 (HUI3). Direct medical costs were collected during one year before and 27 months after start of etanercept and associated with gain in utility.

Results: Mean total direct medical costs after start etanercept were on average 12,318 euro per patient per year compared to 3,695 euro in the year before start. The cost analysis showed that three quarters of total direct medical costs originated from etanercept itself. Other direct medical costs, such as costs concerning hospitalization and concomitant medication, decreased compared to the costs in the period before start of etanercept. Especially a great reduction in frequency of visits to the outpatient clinic was seen. Utility was 0.53 before start of etanercept, according to the multi-attribute utility function of the HUI3 on a scale from 0 (dead) to 1 (perfect health). After 27 months utility was 0.78, which is a utility gain of 0.25. In accordance, also all JIA core set response variables improved significantly over 27 months of etanercept treatment.

Conclusions: Although the costs of etanercept therapy are substantial, the gain in utility is even more impressive. This and the fact that these JIA patients were previously refractory to conventional treatment, and at risk for long-time disability and pain, makes the costs justifiable.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease in childhood, prevalence is about one in 1,000 children.[1,2] JIA can result in irreversible changes in cartilage and bone and long-term functional impairment. Chronic diseases such as JIA usually have high economic impact, as patients will suffer from the disease throughout their whole life. More than 50% of children with JIA enter adulthood with ongoing active disease.[3,4]

Bernatsky et al. analyzed the direct medical costs for children with JIA compared to controls.[5] They concluded that the economic impact of JIA is substantial, and that a higher active joint count is independently associated with greater costs. The relation between active disease and increase in costs was also seen in the study by Minden et al.[6]

Current guidelines require that patients with a polyarticular course are treated with disease modifying anti-rheumatic drugs (DMARDs), usually methotrexate (MTX), when required accompanied by intra-articular or systemic glucocorticoids.[4,7] Since its introduction, etanercept has become an important treatment for patients with JIA refractory to synthetic DMARDs. Several studies have shown an impressive decline of disease activity expressed by the JIA core set of response variables during the treatment with etanercept.[8-14] Etanercept is a high cost medication compared to more traditional drugs such as MTX. On the other side, suppressing disease activity effectively early in the disease course might prevent pain and disability and therefore subsequently reduce costs on the long-term.[15] Therefore, it is important to have more insight on the costs and effects (i.e. utility) of etanercept in JIA.

Our aim was to analyze and report the costs and effects of etanercept therapy in patients with JIA.

METHODS

Patients and data from the ABC-register

In the Netherlands JIA patients are eligible for treatment with etanercept if the disease has a polyarticular course and the response to the maximum (tolerated) dose of MTX is not sufficient. All Dutch JIA patients, younger than 18 years, treated with etanercept are included in the national Arthritis and Biologicals in Children (ABC) register to evaluate long-term effectiveness and safety of etanercept and other biologic agents.[13]

Data on patient and disease characteristics are collected in the ABC-register, including gender, date of birth, date of JIA onset, JIA subtype, medical history, previous medication and data on the use of etanercept such as dose, frequency, use of concomitant drugs and (serious) adverse events. Also disease activity is evaluated and entered into the register at start of treatment, after 3 months, 15 months and every year thereafter. The outcome measures used to assess disease activity consisted of the following set of six response variables of the JIA core set: 1) overall assessment of the disease activity by the physician through the visual analogue scale (VAS) (range 0-100 mm, 0 best score); 2) childhood health assessment questionnaire (CHAQ) (range 0-3, 0 best score) by the patient or parent; 3) overall assessment of well-being by the patient or parent through the VAS (range 0-100 mm, 0 best score); 4) number of active joints (joints with swelling not caused by deformity, or joints with limited motion, and with pain, tenderness, or both); 5) number of joints with limited motion; and 6) a laboratory marker of inflammation, erythrocyte sedimentation rate (ESR).[16]

We prospectively collected additional data on the Health Utilities Index Mark 3 (HUI3) from the patients in the register from 2003 until 2006.[17] Seven of the nine Dutch pediatric rheumatology centers agreed to participate in this add-on study. Parents of eligible patients were asked to complete the HUI3 at the start and after 3, 15 and 27 months of treatment.

The protocol was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam and local Medical Ethical Committee approval was given in every participating center. Written informed consent was obtained, and the study was conducted in accordance with the Declaration of Helsinki.

Cost and effect analysis

We collected data on costs in 12 months prior to start of etanercept treatment and in the 27 months thereafter. From a social perspective there are several costs, which should be taken into account. We collected all direct medical costs retrospectively from paper and electronic patients' files and completed by treating physician inquiry. In addition, parents were asked to fill out cost diaries during etanercept therapy, to estimate direct non-medical costs. However, parents were reluctant to fill out these dairies and due to the bad response (89% missing) we decided to report the direct medical costs only.

Direct medical costs involve expenses incurred directly pertaining to medical care. For instance, costs concerning medication, diagnostic procedures and hospitalization. Direct non-medical costs are primarily related to out-of-pocket expenses incurred by the patient

due to illness (e.g. travel and time expenses; these expenses are related to the disease, but are not *medical* expenses).

Prices for all hospital related costs were based on real prices from the coordinating centre (Erasmus MC Sophia Children's Hospital) and were collected with the assistance of the financial department. Costs for medication were retrieved from the Pharmatherapeutic Compass provided by the Dutch Board of Health Insurances (CVZ).[18] We calculated costs for all drugs with the exact dose of medication and administration period as reported in the patients' files. The base year was 2008 for all costs; costs retrieved from other years were converted to 2008 euros using the consumer Dutch price index rate (www.cbs.nl).

To evaluate the effect of etanercept we used the Health Utility Index mark 3 (HUI3). The HUI3 is a preference-based health-related quality of life (HRQoL) measure that includes a classification system that indicates the level of impairment in eight domains (attributes) based on information retrieved by a 15-item parent questionnaire. These eight single-attributes in the HUI3 are vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, with each five or six levels representing the range of functioning from not (1) to severely impaired (5 or 6). The parents of the JIA patients were asked to complete the HUI3 at start of etanercept, and after 3, 15 and 27 months of therapy. In our study we used the proxy assessment since children are considered to be unable to value health states.[19]

We applied the single- and multi-attribute utility formulas suggested by Feeny et al. for estimating single- and multi-attribute utilities.[20] The latter is scored on a scale from 0 (dead) to 1 (perfect health). The utilities reflect the value of HRQoL measured from the social perspective.

Statistical analysis

All outcomes including means, medians, standard errors and interquartile range (IQR) were calculated using statistical software SPSS 15.0.1. (SPSS Inc., Chicago Illinois, USA).

We compared the characteristics of the 49 patients included in this study with those of the 146 patients that were included in the ABC-register at the end of 2006 using the two-sample-t-test and chi-square test.

We tested if any significant changes were found comparing outcomes of HUI3 questionnaires and disease activity response variables over time using Linear Mixed Models to account for the correlations between the repeated measurements. We inserted disease duration at start of etanercept as a continuous covariance and onset JIA subtype (systemic

and non-systemic JIA) as categorical covariance for all models. Intercept was set as random variable, time of questionnaire assessment, disease duration and JIA subtype as fixed variable. Compound symmetry was defined as covariance structure. We used a level of significance of $p < 0.05$.

RESULTS

Patient and disease characteristics

During the study period 53 JIA patients completed the HUI3 during treatment with etanercept, of which 49 patients continued etanercept treatment for at least 27 months. Four (three systemic and one polyarticular rheumatoid factor positive JIA) patients discontinued etanercept because of inefficacy after a median use of 14.3 months (IQR 3.3-26.7).

Of the 49 patients included in this study the median age at start of etanercept was 11.7 years with median disease duration of 3.6 years. The patient and disease characteristics (table 7.1) are representative for the 146 patients that were included in the ABC-register at the end of 2006.[13] No significant differences between groups were found in disease duration before start of etanercept ($p = 0.16$) or JIA subtype being systemic or non-systemic ($p = 0.56$).

Etanercept was given in the dose of 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly, with the exception of one patient whom received the dose of 0.4 mg/kg three times a week for seven months.[21,22] History of anti-rheumatic drug use and concomitant drug use at start of etanercept are shown in table 7.1.

Cost and effect analysis

Total direct medical costs before start of etanercept therapy were 3,695 euro per patient per year (table 7.2). After start, calculated over a 2.25-year period, mean costs are 12,318 euro per patient per year. More than three quarters of these costs were direct etanercept costs. Most other direct medical costs were reduced compared to the period before start of etanercept; 43% reduction in the period 3 to 15 months after start etanercept and 55% in the period 15 to 27 months after start. The number of visits to the paediatric rheumatologist and other specialists are distinctly lower during etanercept use and also hospitalization costs decrease substantially over time. Costs for DEXA scans were high in the first 3 months after start of etanercept due to study protocol.

Table 7.1: Patient and disease characteristics at start etanercept (N = 49)

Characteristics	Median	(IQR)
Age in years at start ETN	11.6	(7.9-14.6)
Duration JIA in years at start ETN	3.6	(2.0-5.1)
Sex	**N**	**(%)**
Male	20	(41)
Female	29	(59)
Onset subtype JIA		
Systemic	11	(22)
Polyarticular rheumatoid factor positive	4	(8)
Polyarticular rheumatoid factor negative	18	(37)
Oligoarticular extended	11	(22)
Enthesitis related arthritis	2	(4)
Juvenile arthritis psoriatica	3	(6)
History of anti-rheumatic drug use before start etanercept		
NSAID	49	(100)
Glucocorticoids systemic	30	(61)
Glucocorticoids local injection	23	(47)
MTX	49	(100)
Other DMARD	27	(55)
Concomitant drug use at start of etanercept		
NSAID	45	(92)
Glucocorticoids systemic	23	(47)
MTX	39	(80)
Other DMARD	5	(10)

ETN; etanercept, JIA; Juvenile Idiopathic Arthritis, NSAID; Non-Steroid Anti-inflammatory Drug, MTX; Methotrexate, DMARD; Disease Modifying Anti-Rheumatic Drug, IQR; interquartile range

The outcomes of both the HUI3 as the disease activity response variables of the JIA core set are shown in table 7.3.

The gain in utility over the study period is 0.25 on a score from 0 to 1, from start (0.53) to 27 months (0.78) of etanercept treatment.

Table 7.2: Direct medical costs in euros per patient during one year before and 2.25 years after start of etanercept therapy

Mean costs	Before start ETN	After start ETN		
	12 mo to start (1 year)	start to 3 mo (0.25 year)	3 to 15 mo (1 year)	15 to 27 mo (1 year)
Consultation PR at outpatient clinic	493.4	119.2	270.0	212.3
Telephonic consultation PR	34.9	5.5	19.1	14.7
Consultation other specialists*	69.7	8.9	26.4	34.4
Hospital admissions	963.9	0	220.9	100.4
Physiotherapy	393.9	95.6	312.8	208.6
Other paramedical care‡	219.7	51.5	108.1	66.3
Etanercept therapy	0	2,357.4	10,141.1	10,590.3
Other medication#	819.8	267.4	715.8	607.8
Laboratory	273.1	48.9	83.9	77.4
X-ray	356.5	112.0	260.8	263.2
DEXA scan	30.5	134.3	85.4	61.0
Ultrasound	18.9	0	4.6	5.9
MRI	20.8	0	8.5	14.6
TOTAL in period	**3,695.1**	**3,200.7**	**12,257.4**	**12,256.9**
Mean cost per month	**307.9**	**1,066.9**	**1,021.5**	**1,021.4**

*Ophthalmologists, dermatologists, orthopedists/ orthopedic surgeons, emergency care doctors, paediatricians, orthodontists, ear nose and throat doctors, oral surgeons, and neurologists

‡ Occupational therapy, rehabilitation therapy, and psychotherapy

Including NSAIDs, glucocorticoids systemic and intra-articular, and synthetic DMARDs, but also other medication related to JIA such as folic acid and omprazole

ETN; etanercept, Mo; months, PR; paediatric rheumatologist

As we previously showed, the HUI3 improves on all utility functions impaired by JIA, but seems less sensitive for changes on "Emotions" as compared to the CHAQ and Child Health questionnaire.[17]

Table 7.3: Disease activity and outcomes on the HUI3 in 49 JIA patients during treatment with etanercept

Parameters	Start	3 months	15 months	27 months	
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	p-Value
JIA core set					
VAS physician (0-100mm)	66.0± 2.5	14.9± 2.5	13.2± 2.7	11.4± 3.0	<0.001
Number of active joints	16.7± 1.0	3.99± 1.0	2.39± 1.0	2.45± 1.1	<0.001
Number of limited joints	10.9± 0.7	5.40± 0.7	3.00± 0.8	2.89± 0.8	<0.001
ESR (mm/h)	26.8± 2.0	11.9± 2.0	10.9± 2.1	11.1± 2.4	<0.001
CHAQ Disability Index (0-3)	1.70± 0.1	1.00 ± 0.1	0.60± 0.1	0.50± 0.1	<0.001
VAS pain (0-100mm)	53.8± 3.2	15.7± 3.2	12.6± 3.5	11.7± 3.8	<0.001
VAS well-being (0-100mm)	50.8± 3.4	15.7± 3.4	12.4± 3.6	15.2± 3.9	<0.001
HUI3 (0-1)					
Single-attribute utility functions					
Vision	0.99± 0.00	0.99± 0.00	0.99± 0.00	0.99± 0.00	n/a
Hearing	1.00± 0.00	1.00± 0.00	1.00± 0.00	1.00± 0.00	n/a
Speech	0.99± 0.00	0.99± 0.01	0.99± 0.01	1.00± 0.01	0.39
Ambulatory	0.92± 0.01	0.96± 0.02	0.96± 0.02	0.96± 0.02	0.02
Dexterity	0.92± 0.01	0.95± 0.02	0.97± 0.02	0.97± 0.02	0.02
Emotions	0.97± 0.01	0.96± 0.01	0.98± 0.02	0.98± 0.02	0.51
Cognition	0.97± 0.01	0.97± 0.02	0.98± 0.02	0.98± 0.02	0.69
Pain	0.81± 0.02	0.91± 0.02	0.90± 0.03	0.94± 0.03	<0.001
Multi-attribute utility function	0.53± 0.04	0.69± 0.05	0.74± 0.06	0.78± 0.07	0.001

CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate, HUI3: Health Utilities Index Mark 3; n/a: not applicable (since the scores remained unchanged over time), SE: Standard error of the mean; VAS; Visual Analogue Scale

DISCUSSION

If severe JIA is not treated effectively it can lead to irreversible damage to the joints, long-term disability and other serious problems such as growth inhibition. As previously reported, etanercept not only suppresses disease activity in JIA patients, but also improves HRQoL.[13,17] However, it is an expensive treatment drug. Results from the current cost analysis show that

the total direct cost per year before start of etanercept therapy was 3,695 euro per patient, and approximately 12,317 euro per patient per year after start of etanercept. Our study indicated that etanercept itself accounts for more than three quarters of the direct medical costs, when JIA patients are treated with this drug. Other direct medical costs decreased during etanercept therapy with 55% after 27 months of etanercept therapy. Although this was not seen yet in the first three months of etanercept use; probably partly due to extra monitoring costs. The number of visits to the paediatric rheumatologist and other specialist were distinctly lower during etanercept use and also hospitalization costs decreased substantially over time.

HRQoL measures provide important information on the burden of JIA and the improvements offered by new treatments.[15] Although we previously published outcomes on the HUI3 from 53 JIA patients in the ABC-register, we shortly described results from 49 of these patients again to provide crucial information on the quality of the treatment effect.[17] The 49 patients, who used etanercept for at least 27 months, showed an impressive utility gain of 0.25 (from 0.53 to 0.78 on a scale from 0 to 1). All domains impaired by JIA improved during etanercept, although the domain "Emotions" seemed less sensitive to detect changes compared to other HRQoL measures.[17] Encouraging was that we did not only find a utility improvement after 3 months and 15 months of treatment, but even an additional strong improvement after 27 months.

Thornton et al. demonstrated in their study in JIA patients that visits to the paediatric rheumatologist account for the largest component of the total costs during the first year after diagnosis.[23] Being able to lower these costs, as demonstrated in our study, is therefore profitable. Other studies have reported on the costs of etanercept. A cost-utility analysis was undertaken as part of the manufacturer's submission. For a patient started on etanercept rather than placebo, the incremental benefit estimated per patient was 1.74 quality adjusted life year (QALY). Cost per QALY was £16,082 (range £3,900 - £34,000).[24] However, their model was based on a model for RA and contained a large number of strong assumptions, which made accuracy of the estimate questionable. In addition, in daily practice paediatric rheumatologists choose between etanercept and conventional drugs, not placebo. Our study represents real life data over a longer period of time and no assumptions were made. A study from Finland retrospectively collected costs from 31 JIA patients from medical records and by interviewing parents before and during etanercept treatment.[25] They also showed an increase in direct medical costs due to use of etanercept, compared to the prevailing treatment, but also showed a decrease in indirect costs of 50%. However, they did not gather information on utility of etanercept therapy and did not compare costs of therapy with effect.

Patients in our study had already relatively high direct medical costs before start of etanercept compared to costs from patients reported in other studies on JIA.[5,6] This suggests what also has been reported in literature: the severity of JIA is related to the height of medical costs, since patients in our study were refractory to therapy previous to etanercept therapy and had high disease activity before start of etanercept.[5,6]

Our study had some limitations. First of all, we only captured direct medical costs. Although we did not captured indirect costs and direct non-medical costs, we expect that these costs are minimal in comparison with the direct medical costs.[15] Secondly, costs were retrospectively collected from patients' files and electronic records rather than prospectively through cost questionnaires. However, the information on direct medical costs retrieved from the files proved to be complete and accurate. Thirdly, we did a separate cost and utility analysis. Ideally, costs and utilities would be compared with a control-group. However, since etanercept has proven to be very successful in JIA patients refractory to synthetic DMARDs including MTX, this would not be ethical. Fourthly, this study was done in Dutch JIA patients and treatment was given to the preference of the treating physician. Therapeutic strategies may vary from other countries and therefore also costs can vary.

The goal of etanercept treatment is rapid remission of JIA to prevent long-term disability and pain. Therefore calculating costs and utility over a 2.25 year period might not be sufficient to evaluate the full benefit of etanercept therapy. Since we showed in a previous study that it is possible to induce remission in refractory JIA patients with etanercept and subsequently that this medication can be successfully discontinued if a patient is in clinical remission for more than 1.5 year, medical costs on the long-term maybe lower compared to conventional treatment.[26] The next step is to estimate lifetime utility gain and compare long-term benefits of etanercept therapy with overall medical costs.

In general, many studies reported on the effectiveness and safety of new drugs in treatment of JIA. The introduction of biologicals have let to substantially higher drug costs.[15] However, these costs should be compared to the reduction of pain and prevention of irreversible damage to the joints and lifelong disabilities.

The results from our cost analysis indicate that although etanercept is expensive, it is an important intervention for JIA patients previously refractory to treatment, since it can establish great utility gain in only a short period of time, which may prevent medical cost in the future.

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Part 4

Treatment Strategies

Chapter 8

The frequency of administration of etanercept in Juvenile Idiopathic Arthritis

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Initiating etanercept in a once weekly dose in children with Juvenile Idiopathic Arthritis

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ABSTRACT

Objective: To evaluate the effectiveness of etanercept in the double dose of 0.8 mg/kg SC once weekly.

Methods: Patients with JIA in remission, who prior to the study used the dose of 0.4 mg/kg SC twice weekly, received etanercept in the double dose of 0.8 mg/kg SC once weekly. In addition, etanercept was initiated in patients in the once weekly double dose. Disease activity was evaluated by means of seven response variables at the start of the study and re-evaluated after three months.

Results: After three months, eleven patients, who were in remission at the start of the study, showed values of the response variables which were equal to the values at the start of the study. No flares were seen. Six patients, in whom etanercept in the double dose once weekly was initiated, showed major improvement on the response variables.

Conclusions: The administering of a once weekly double dose etanercept is effective to retain remission in patients with JIA. A once weekly double dose of etanercept can induce inactive disease of JIA.

INTRODUCTION

Etanercept has shown to be effective in Juvenile Idiopathic Arthritis (JIA).[1-4] In the current treatment, etanercept is administered subcutaneously in the dose of 0.4 mg/kg (with a maximum of 25 mg) twice weekly. Clinical trials in Rheumatoid Arthritis and Ankylosing Spondylitis show that the administering of an once weekly double dose is effective enough to induce and retain remission in adults.[5,6] A pharmacokinetic model developed by Yim et al. shows that the computer simulated concentrations of etanercept in children of 0.8 mg/kg SC once weekly dosing has widely overlapping concentration profiles with the usual dosing regimen of 0.4 mg/kg SC twice weekly at steady state.[7] In addition, previous studies demonstrate that is safe to administer the high dose of 0.8 mg/kg SC twice weekly to children.[8] Wallace mentions the double dose of 0.8 mg/kg once weekly as a possible administration of etanercept in patients with JIA, but this is not supported by literature.[9] To date, no clinical trials in administering etanercept in the dose of 0.8 mg/kg SC once weekly in patients with JIA have been reported.

The aim of this study was to evaluate if etanercept in the once weekly dose of 0.8 mg/kg SC (with a maximum of 50 mg) is just as effective as the twice weekly dose of 0.4 kg/mg SC to keep patients with JIA in remission and induce inactive disease.

METHODS

Patients with JIA who already had been treated with etanercept twice weekly in the usual dose of 0.4 mg/kg SC were included and switched to the double dose of 0.8 mg/kg SC once weekly. Patients had to be in remission according to the criteria of Wallace et al.[10] These remission criteria state that inactive disease had to persist for more than six months and inactive disease is defined as: no active arthritis, no fever, rash, serositis or generalized lymphadenopathy attributable to JIA, no active uveitis, normal ESR and a physician's overall assessment of disease activity that indicated no disease activity.

On the other hand patients were included, who were not yet on treatment with etanercept. In these patients etanercept was initiated in the double dose of 0.8 mg/kg SC once weekly at the start of the study.

Data collected were patient and disease characteristics as age, gender, disease duration, subtype of JIA, duration of etanercept therapy prior to the study, adverse advents during the study and co-medication.

The outcome measures used to assess disease activity consisted of the following set of seven response variables: 1) global assessment of the disease activity by the physician by means of the visual analogue scale (VAS) (range 0-100 mm), 2) children health assessment questionnaire (CHAQ) (range 0-3) by the patient, 3) global assessment of pain by the patient or parent by means of the VAS (range 0-100 mm), 4) global assessment of well-being by the patient or parent by means of the VAS (range 0-100 mm), 5) number of active joints (joints with swelling not due to deformity or joints with limitation of motion and with pain, tenderness, or both), 6) number of joints with limitation of motion, and 7) a laboratory marker of inflammation; erythrocyte sedimentation rate (ESR). Patients were evaluated by means of these seven variables at the start of the study and re-evaluated after three months.

We used the remission criteria by Wallace et al. to evaluate patients after three months.[10] Efficacy was assessed using the American College of Rheumatology Paediatric 30, 50, 70, 90 and 100 criteria (ACR Pedi 30, 50 , 70, 90, 100).[11] This definition states that there should be at least 30% improvement (50%, 70%, 90% or 100% dependent on the score) from baseline in three of any six response variables (not included the VAS pain) in the JIA core set with no more than one of the remaining variables worsening by > 30%. For the evaluation of disease flare we used the definition by Brunner et al.[12] A disease flare was defined as worsening in two of any six response variables (not included the VAS pain) by more than 40% without improvement in more than 1 of the remaining response variables by at least 30%.

RESULTS

Table 8.1 summarizes 11 patients, in whom the administration of etanercept from the usual dose twice weekly was switched into the double dose once weekly. Notable is the equality between the response variables at the start of the study and the response variables after three months. All patients were still in remission after three months. None of the patient had a flare during the three-month course of the study.

Patient 2 and 6 reported headache during the course of the study.

Patient 10 gave a high CHAQ score and high VAS score's of global assessment of pain and well being at the start of the study and after three months, but the disease characteristics are in accordance with the criteria of remission. The CHAQ-score and the VAS score of global assessment of pain did improve during the three-month course of the study.

Table 8.2 summarizes 6 patients in whom a once weekly double dose of etanercept was initiated. Notable is the improvement on all the response variables, even the number of joints with limitation of motion in four patients. Improvements in patients meet the requirements of the definition of improvement of at least the ACR Pedi 50.[11]

DISCUSSION

The results indicate that etanercept administered once weekly in the dose of 0.8 mg/kg SC, is just as effective to keep patients with JIA in remission as in the twice weekly in the dose of 0.4 kg/mg SC. Patient's 10 high VAS score's of global assessment of pain and well-being high score are most likely related to the known emotional disturbances in this patient, as the patient had no disease activity. At least, the outcomes did not worsen after the switch to the once weekly dosing regime.

Six patients, in whom a once weekly dose of etanercept was initiated, showed a major improvement on disease activity. Even the number of joints with limitation improved in four out six patients. Lovell et al. modified this variable in their study to excluded joints with contractures that might not have improved during the short course of treatment suggesting this is not a quick response variable and therefore not a good marker for short-term studies.[1]

There were no serious adverse advents, which confirm the safety of the double dose etanercept.

We had the limitation of a small patient group. A second limitation was that it concerns an open-label study instead of a double-blind study. However, a double-blind comparison of the two regimens would require a number of patients with JIA that is almost impossible to recruit. The follow-up time is relatively short and could therefore be seen as a limitation. However, the study of Yim et al. indicates that etanercept in the 0.8 mg/ kg SC once weekly dosing has widely overlapping concentration profiles with the usual dosing regimen of 0.4 mg/kg SC twice weekly at steady state.[7] The pharmacokinetic steady state of etanercept is reached after 2 weeks. According to Lovell et al. the median time to disease flare with placebo is 28 days, as

Table 8.1: Data from patients, switched from twice weekly usual dose to once weekly double dose etanercept; at start of study/ after 3 months

No. patient	Gender	Age (years)	Disease duration (years)	Subtype	Etanercept use (years)	Co-medication at start study
1	Male	15.0	9.5	sJIA	4.4	
2	Male	12.4	8.3	sJIA	4.3	
3	Female	15.1	9.6	sJIA	4.7	15 mg MTX/ week, NSAID
4	Male	18.2	9.9	pJIA RF +	0.4	5 mg MTX/ week
5	Female	13.5	3.4	pJIA RF -	0.8	
6	Female	14.5	8.4	pJIA RF -	1.4	7.5 mg MTX/ week, NSAID
7	Female	12.9	2.9	pJIA RF -	1.3	
8	Female	11.9	3.5	pJIA RF -	0.6	
9	Male	17.0	8.0	oJIA ext	2.1	
10	Male	10.6	4.9	oJIA ext	1.3	
11	Female	8.5	2.0	PsJIA	0.9	5 mg MTX/ week
mean		13.6	6.4		2.0	

sJIA, systemic JIA; pJIA RF +, polyarticular rheumatoid factor positive JIA; pJIA RF -, polyarticular rheumatoid factor negative JIA; oJIA ext, oligoarticular extended JIA; PsJIA, juvenile arthritis psoriatica;

compared with more than 116 days with etanercept.[1] So three months follow-up should give a realistic outcome of changes due to switching the dosing regime of etanercept.

Although therapies in adults cannot automatically be copied in children, our study shows that findings in the etanercept administration in children are inline with the etanercept therapy in adults.

Concluding, our clinical study supports what has been reported in theory in the literature, namely that the once weekly double dose of etanercept is just as effective to retain remission in patients with JIA. Considering the perfect outcome in the six patients, in whom etanercerpt in the double dose once weekly was initiated, it can even induce inactive disease in patients with JIA.

Co-medication after 3 months	VAS physician (0-100 mm)	CHAQ (0-3)	VAS pain (0-100 mm)	VAS well-being (0-100 mm)	# active joints	# limited joints	ESR (mm/ h)
	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	2 / 1	2 / 5
	0 / 0	0.1 / 0	21 / 2	0 / 2	0 / 0	2 / 0	4 / 6
15 mg MTX/ week, dose NSAID lowered	0 / 0	0.1 / 0.1	3 / 2	2 / 5	0 / 0	5 / 5	2 / 8
MTX stopped	0 / 0	0 / 0	0 / 2	0 / 1	0 / 0	3 / 2	3 / 10
	0 / 0	0.3 / 0.3	0 / 0	0 / 0	0 / 0	2 / 1	5 / 3
7.5 mg MTX/week, NSAID	3 / 9	0.3 / 0.3	1 / 6	0 / 4	0 / 0	12 / 12	3 / 12
	0 / 0	0 / 0	0 / 0	2 / 1	0 / 0	4 / 0	17 / 12
	0 / 0	0 / 0	0 / 12	0 / 0	0 / 0	2 / 1	9 / 20
	0 / 0	0 / 0.3	3 / 0	2 / 3	0 / 0	6 / 7	1 / 2
	0 / 0	0.8 / 0.1	67 / 48	38 / 41	0 / 0	1 / 0	3 / 5
5 mg MTX/ week	0 / 0	0.1 / 0.4	0 / 7	0 / 0	0 / 0	0 / 0	2 / 5
	0.27 / 0.82	0.15 /0.136	8.64 / 6.61	4 / 5.18	0 / 0	3.55 / 2.64	4.18 / 8

Table 8.2: Data from patients, in whom etanercept therapy was initiated in once weekly double dose; at start of study / after 3 months

No. Patient	Gender	Age (years)	Disease duration (years)	Subtype	Co-medication at start study	Co-medication after 3 months
12	Female	17.3	5.0	pJIA RF +	25 mg MTX/week, NSAID	MTX stop, NSAID
13	Female	14.3	1.4	pJIA RF +	25 mg MTX/week, prednisone, NSAID	15 mg MTX/week, prednisone, dose NSAID lowered
14	Female	14.4	3.2	pJIA RF -	25 mg MTX/week, NSAID	10 mg MTX/week, NSAID equal
17	Male	7.3	0.7	pJIA RF -	25 mg MTX/week, prednisone, NSAID	15 mg MTX/week, prednisone, dose NSAID lowered
15	Male	12.0	0.9	PsJIA	10 mg MTX/week, NSAID	7.5 mg MTX/week, NSAID stop
16	Female	14.0	2.5	PsJIA	25 mg MTX/week	20 mg MTX/week

sJIA, systemic JIA; pJIA RF +, polyarticular rheumatoid factor positive JIA; pJIA RF -, polyarticular rheumatoid factor negative JIA; oJIA ext, oligoarticular extended JIA; PsJIA, juvenile arthritis psoriatica; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale; CHAQ, children's health assessment questionnaire; ACR Pedi 50, 70, 90, 100, American College of Rheumatology Pediatric 50, 70, 90, 100-score

Best improvement criteria met	VAS physician (0-100 mm)	CHAQ (0-3)	VAS pain (0-100 mm)	VAS well-being (0-100 mm)	# active joints	# limited joints	ESR (mm/h)
	58 / 16	2.5 / 1.5	100 / 13	61 / 1	35 / 11	14 / 14	38 / 34
ACR Pedi50	**72%**	**40%**	**87%**	**98%**	**69%**	**0%**	**11%**
	83 / 0	2.4 / 0	81 / 0	98 / 0	23 / 0	5 / 5	4 / 2
ACR Pedi100	**100%**	**100%**	**100%**	**100%**	**100%**	**0%**	**50%**
	52 / 14	1.4 / 0.6	71 / 0	53 / 0	36 / 7	19 / 1	32 / 22
ACR Pedi70	**73%**	**57%**	**100%**	**100%**	**81%**	**95%**	**31%**
	50 / 4	1 / 0.1	3 / 12	64 / 36	11 / 0	1 / 0	8 / 10
ACR Pedi90	**92%**	**90%**	**-75%**	**44%**	**100%**	**100%**	**-25%**
	45 / 8	0.5 / 0.5	13 / 13	10 / 4	14 / 3	4 / 3	7 / 7
ACR Pedi50	**82%**	**0%**	**0%**	**60%**	**79%**	**25%**	**0%**
	49 / 4	1.4 / 0.1	70 / 2	62 / 2	16 / 0	17 / 1	5 / 5
ACR Pedi90	**92%**	**93%**	**97%**	**97%**	**100%**	**94%**	**0%**

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Chapter 9

Discontinuation of etanercept in Juvenile Idiopathic Arthritis patients after successful therapy

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ABSTRACT

Objective: The aim of etanercept therapy in Juvenile Idiopathic Arthritis (JIA) is to achieve disease remission. Little is known about when or how to stop etanercept when this aim is reached. Our objective was to describe the disease course of JIA patients who discontinued etanercept because of a sustained good clinical response.

Methods: The Arthritis and Biologicals in Children (ABC)-project is the Dutch national register on biologicals in JIA, in which data are collected prospectively. All patients who discontinued etanercept because of a sustained good clinical response were selected. For disease course evaluation we used the Wallace criteria for clinical remission on and off medication.

Results: From the patients in the ABC-register 19 discontinued etanercept because of a sustained good clinical response. After discontinuation ten patients (53%) had retained remission during a median of 0.8 years. They had used etanercept longer (3.5 vs. 2.1 years, $p = 0.21$) and showed a longer median period of clinical remission on medication (1.5 vs. 0 years, $p = 0.004$) compared to the nine patients who flared. Four out of five patients who discontinued etanercept without tapering flared, all other patients tapered the dose or frequency before discontinuation. All eight patients who resumed etanercept use after flaring reacted promptly to treatment.

Conclusions: Meeting the clinical remission criteria on etanercept for a longer period correlates with a better chance of retaining remission after discontinuation. Most patients who discontinued etanercept without tapering had a disease flare. Good responses to restart of etanercept after flaring were observed.

INTRODUCTION

Etanercept is currently the most frequent prescribed biological, and in the Netherlands the only one registered for the treatment of Juvenile Idiopathic Arthritis (JIA). It is proven to be effective in JIA and a substantial part of the JIA patients has a sustained good clinical response on etanercept.[1-5] After reaching remission, it is a logical step to try to reduce or discontinue etanercept in order to reduce the burden of the weekly injections and prevent unnecessary side-effects and costs.[6-8] However, no guidelines on when or how to stop etanercept therapy are currently available and little is known about the course of the disease in JIA patients after discontinuation.[9] Also, data on Rheumatoid Arthritis (RA) treatment on this subject are limited.[7,8]

The Arthritis and Biologicals in Children (ABC)-project is a Dutch national study to evaluate etanercept and other biologicals used in JIA.[4] In this project several patients who had a sustained good clinical response discontinued etanercept. Our aim was to describe patient and disease characteristics of these patients and to investigate the course of the disease after discontinuation of etanercept.

PATIENTS AND METHODS

Subjects and study design

This study is embedded in the ABC-project. The ABC-project is a prospective ongoing multicentre, observational study which is coordinated by the Erasmus MC Sophia Children's Hospital and includes all Dutch JIA patients who used etanercept since 1999.[4,10] The protocol was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam. Written informed consent was obtained, and the study was conducted in accordance with the Declaration of Helsinki.

From the ABC-register we selected all patients who had discontinued the etanercept treatment because of a sustained good clinical response as judged by the treating physician.

In the ABC-register data were prospectively collected at start of etanercept, after three months of therapy and every year thereafter. The following data were available from these fixed follow-up moments in the register: patient and disease characteristics including gender, age at onset of JIA, age at start of etanercept use, disease duration, subtype of JIA, duration of

etanercept therapy and dose, concomitant drug use and disease activity. Changes in etanercept use were collected on a continuous basis in the register.

For this study, additional detailed data were retrospectively collected from the patient files: concomitant drug use right before and after discontinuation of etanercept therapy, disease activity at the time of and after discontinuation of etanercept including systemic features, duration of remission, disease flares between the fixed follow-up moments, possible reasons for disease flaring and treatment after flaring.

The outcome measures used to assess disease activity consisted of the following JIA core set of six response variables: global assessment of disease activity by the physician and of well-being by the patient both by means of a visual analogue scale (VAS), Children Health Assessment Questionnaire (CHAQ), number of active joints, number of limited joints, and erythrocyte sedimentation rate (ESR).[11]

Analysis of disease course

Achievement of a sustained good clinical response was determined by the treating physician. The decision to discontinue treatment for this reason could be on the initiative of the treating physician but also on initiative of the patient.

To evaluate the disease course more objectively we used the criteria for inactive disease either on medication (IDM) or off medication (ID) by Wallace et al. These criteria were defined as: no active arthritis, no fever, rash, serositis or generalized lymphadenopathy attributable to JIA, no active uveitis, normal ESR and a physician's overall assessment of disease activity that indicated no disease activity.[12,13] We defined ESR values under 16 mm/hour as normal. We stated that a physician's overall assessment score below the 10 mm on the VAS indicated no disease activity.

In case of clinical remission on medication (CRM) criteria of IDM had to be met for more than six months. In case of clinical remission off medication (CR) criteria for ID had to be met for more than twelve months.[12,13] Although the remission criteria by Wallace et al. were not specifically developed for the JIA subtypes Juvenile Arthritis Psoriatica (PsJIA) or Enthesitis Related Arthritis (ERA), we still used these criteria to evaluated disease activity in patients with these subtypes since no other remission criteria are currently available. In addition, it was noted if psoriatic lesions or active entheses were presented.

A disease flare was defined as an increase in disease activity as stated by the treating physician, which subsequently meant the end of the remission period.

Statistical analysis

Baseline characteristics were listed and summarised and medians accompanied by interquartile range (IQR) were calculated. Response variables were evaluated according to the remission criteria by Wallace et al.. The Mann-Whitney test was used to compare time periods (using level of significance $p < 0.05$). Analyses were performed using the SPSS for Windows package, version 15.0.1..

RESULTS

Patient and disease characteristics and drug use

By the end of January 2008 210 patients, either responders or non-responders, were included in the ABC-register.[4] Of these patients 19 had discontinued etanercept because they had a sustained good clinical response according to their treating physician. Patient and disease characteristics are summarised in table 9.1 and are representative for the patients included in the ABC-register.[4] Median etanercept dose at start was 0.83 mg/kg/week, two patients with systemic JIA did not reach a good clinical response on this initial dose, after three months their dose was raised to 1.6 mg/kg/week. None of the patients developed uveitis during the course of the disease.

During treatment with etanercept all co-medication was discontinued in seventeen patients; patient 7 and 15 still used co-medication (MTX) at the moment etanercept was discontinued.

Six patients took the initiative themselves to discontinue etanercept. Patient 6 and 7 had developed an aversion against the injections and severe local irritation at the injection site. Five patients discontinued etanercept therapy without tapering. The other patients first reduced the etanercept dose or injection frequency before complete discontinuation. Characteristics and disease course of each individual patient are shown in table 9.2.

Disease course after discontinuation of etanercept

Ten patients retained a good clinical response after discontinuation of etanercept during a median follow-up of 0.8 years (IQR 0.5-2.8), nine patients developed a disease flare within a median of 0.7 years (IQR 0.1-1.1) after discontinuation of etanercept. None of the PsJIA patients had psoriatic lesions and the ERA patient did not have active entheses.

The ten patients with ID or CR at the last observation, used etanercept during a median period of 3.5 years (IQR 1.9-5.1) versus 2.1 years (IQR 1.2-3.8) in patients who developed a disease flare ($p = 0.21$). The median CRM time was respectively 1.5 years (IQR 0.3-2.8) versus 0 years (range 0-0.2), this is statistically significant different ($p = 0.004$). The ten patients who retained a good clinical response were all in remission according to criteria for CRM at the moment of discontinuation etanercept therapy. At the last observation four of the ten had reached the criteria for CR after discontinuation of etanercept.

Table 9.1: Overall patient and disease characteristics (N=19)

Characteristics	**Median**	**(IQR)**
Age at JIA onset (years)	7.5	(4.2-9.9)
Age at start etanercept (years)	10.7	(9.4-14.5)
Disease duration at start etanercept (years)	3.4	(1.6-5.2)
Etanercept dose at start (mg/kg/week)	0.83	(0.71-0.88)
Onset subtype JIA	**N**	**(%)**
Systemic	5	(26)
Polyarticular rheumatoid factor positive	2	(11)
Polyarticular rheumatoid factor negative	5	(26)
Oligoarticular extended	3	(16)
Juvenile arthritis psoriatica	3	(16)
Ethesitis related arthritis	1	(5)
History of drug use before start etanercept		
NSAIDs	19	(100)
Glucocorticosteroids	11	(58)
MTX	19	(100)
Other DMARDS	12	(63)
Use of other concomitant drugs at start etanercept		
NSAIDs	15	(79)
Glucocorticosteroids	9	(47)
MTX	10	(53)
Other DMARDS	3	(16)

JIA, Juvenile Idiopathic Arthritis; NSAID, Non-Steroid Anti-Inflammatory Drug; DMARD, Disease Modifying Anti-Rheumatic Drug; MTX, Methotrexate

Seven of the nine patients who experienced disease flaring did not meet the CRM criteria at the moment they discontinued etanercept therapy. In the six months before discontinuation patient 9 and 19 still showed minimal arthritis activity, patient 13 had a physician's overall assessment of disease activity above 20 mm and patients 6, 7, 8 and 16 had an ESR above 16 mm/hour.

Possible explanations for developing a disease flare, besides etanercept discontinuation, were infections in two patients (patient 8 and 19).

After developing a disease flare eight patients restarted etanercept therapy, from whom five also restarted NSAIDs, two systemic glucocorticoids and two MTX as concomitant medication. All of these patients regained a good clinical response on etanercept and seven met the criteria for IDM within a half year after restarting etanercept, patient 6 within 1.5 year. Patient 8 was hospitalized because of a gastroenteritis and did not restart etanercept therapy.

DISCUSSION

We evaluated all 19 JIA patients from the ABC-register who discontinued etanercept because of a sustained good clinical response. Ten of these patients still met the criteria of ID at the last observation, four even reached CR. We investigated if these patients had significant different patient or disease characteristics in comparison to patient who had a disease flare after etanercept discontinuation. The results indicate that patients with a longer remission period according to criteria of CRM have a better chance of retaining inactive disease after discontinuation of etanercept ($p = 0.004$). Since the ten patients who maintained remission had a median CRM time of 1.5 years, we suggest that JIA patients should meet the criteria of CRM for at least 1.5 years before considering discontinuation of etanercept.

Predicting clinical outcome in JIA patients is difficult given the heterogeneity of the disease and it is difficult to determine whether a patient is in complete remission. For instance Foell et al. suggest that even in the absence of clinical signs residual synovial inflammation might be the cause for relapses in JIA patients after discontinuation of drugs.[14] Therefore in our study we not only considered the judgement of the treating physician but also used the remission criteria of Wallace et al. for CRM and CR to evaluate the patients more objectively.

Table 9.2: Individual characteristics and disease course of JIA patients with a sustained good clinical response who discontinued etanercept

No. patient	JIA subtype	Sex	Disease duration at start (years)	Time on therapy (years)	Initiative to stop	Tapering of ETN before stop	IDM # (years)	CRM # (years)	ID # (years)	CR # (years)	Time to flare after stop (years)	Disease course and therapy after stop
1	sJIA	M	4.0	5.2	PH	yes	2.4	1.9	1.6	0.6		Remission
2	sJIA	F	3.2	5.3	PH	yes	2.6	2.1	0.8	0	0.76	FLARE; restart NSAID and ETN
3	sJIA	M	2.8	3.7	PH	yes	3.0	2.5	0.4	0		Remission
4	sJIA	M	11.5	5.1	PT	yes	4.4	3.9	0.6	0		Remission
5	sJIA	M	5.2	6.5	PH	yes	4.7	4.2	0.5	0		Remission
6	JIA RF+	F	4.8	0.6	PT	no	0	0	0	0	0.25	FLARE; restart NSAID, MTX and ETN
7	JIA RF+	F	2.0	1.1	PT	no	0	0	0	0	0.18	FLARE; restart ETN and continue MTX
8	JIA RF-	M	5.2	3.8	PH	yes	0	0	1.30	0.30	2.25	FLARE; hospitalisation, restart NSAID and prednisolone
9	JIA RF-	M	5.3	1.0	PH	no	0	0	0	0	0.04	FLARE; restart prednisolone and ETN
10	JIA RF-	F	0.5	2.4	PH	yes	0.7	0.2	2.8	1.8		Remission
11	JIA RF-	F	1.6	2.1	PH	yes	1.6	1.1	0.4	0		Remission
12	JIA RF-	F	11.1	3.6	PT	yes	2.9	2.4	2.8	1.8		Remission
13	oJIA ext	M	8.8	2.1	PH	yes	0.3	0	0.1	0	0.05	FLARE; restart NSAID and ETN
14	oJIA ext	F	3.4	1.6	PH	yes	0.8	0.3	4.5	3.5		Remission
15	oJIA ext	F	1.4	1.7	PT	no	1.4	0.9	1.0	0		Remission
16	PsJIA	F	0.4	2.5	PT	no	0	0	0	0	0.62	FLARE; hospitalisation, restart prednisolone, MTX and ETN

Table 9.2: Continued

No. patient	JIA subtype	Sex	Disease duration at start (years)	Time on therapy (years)	Initiative to stop	Tapering of ETN before stop	IDM # (years)	CRM # (years)	ID # (years)	CR # (years)	Time to flare after stop (years)	Disease course and therapy after stop
17	PsJIA	M	2.8	2.0	PH	yes	0.8	0.3	0.5	0		Remission
18	PsJIA	M	4.6	1.6	PH	yes	0.8	0.3	0	0	0.03	FLARE; restart ETN
19	ERA	M	0.8	3.7	PH	yes	0	0	0	0	0.68	FLARE; restart NSAID and ETN

sJIA, systemic JIA; pJIA RF +, polyarticular rheumatoid factor positive JIA; pJIA RF -, polyarticular rheumatoid factor negative JIA; oJIA ext, oligoarticular extended JIA; PsJIA, juvenile arthritis psoriatica; ERA, enthesitis-related arthritis; IDM, inactive disease on medication; CRM, clinical remission on medication; ID, inactive disease off medication; CR, clinical remission off medication; M, male; F, female; PH, physician; PT, patient; NSAID, Non-Steroid Anti-Inflammatory Drug; DMARD, Disease Modifying Anti-Rheumatic Drug; MTX, Methotrexate; ETN, etanercept # According to the criteria of Wallace et al.[12,13]

Since no exact numbers were given in the criteria by Wallace et al. we defined the values for normal ESR and no disease activity on the VAS of the physician's overall assessment in our protocol.[4] We did not choose 0 mm as best possible score on the VAS since it is to restrictive and therefore chose the threshold value of lower than 20 mm. This choice is based on findings in the ABC-register.[4]

Another result of this study may be that patients should not discontinue etanercept therapy at once, because it seems to be related with a higher risk of developing a disease flare. This is conform the guidelines from RA treatment.[7]

The fact that all eight patients who restarted etanercept after disease flaring regained a good clinical response is reassuring. The characteristics of the disease flares decreased immediately after the restart of etanercept.

The study population was too small to show great differences between the JIA subtypes. Although interesting is that two patients with rheumatoid factor (RF) positive polyarticular JIA did not meet the Wallace criteria, although they had a sustained good clinical response according to the judgement of the treating physician, and developed a disease flare in a relatively short time period after discontinuation of etanercept. This is inline with data from the literature on RA were RF negativity was found to be one of the best independent predictors of remission (RF positivity; OR 0.6 95% CI 0.4-0.96).[15]

A promising result for the systemic JIA (sJIA) patients is that four out of five systemic JIA patients retained ID after discontinuation of etanercept. This result indicates that etanercept can be very successful in sJIA. We already showed in results from our ABC-register that, although there is initially a lower response rate to etanercept, the same percentages of sJIA patients meet the criteria of CRM compared to other subtypes after prolonged time.[4]

Although predicting outcome in patients with JIA is difficult, this explorative study may show some important indicators in the prediction of the disease course after discontinuation of etanercept because of a sustained good clinical response. The evaluation of these indicators is important since no guidelines are yet available on when or how to stop etanercept after successful treatment. According to our observations patients should meet the criteria of CRM and the etanercept dose should be tapered before total discontinuation of etanercept. Also, patients who use etanercept therapy longer and are longer in CRM (at least 1.5 years) have a better chance of retaining ID and reaching CR after discontinuation.

Findings from our observational study may support clinical decision making and can be the basis for future clinical trails.

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Chapter 10

Continuation of etanercept in Juvenile Idiopathic Arthritis patients when therapy is less successful

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Delayed clinical response in patients with Juvenile Idiopathic Arthritis treated with etanercept

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ABSTRACT

Objective: To evaluate response in Juvenile Idiopathic Arthritis (JIA) patients who failed to meet response criteria at 3 months of etanercept treatment.

Methods: Prospective ongoing multicentre, observational study of all Dutch JIA patients using etanercept. Response according ACR Pediatric 30 criteria assessed at start, 3 and 15 months.

Results: Total 179 patients, 70% female, median age onset 5.8 years. 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 initially not responding patients justifies to consider continuation of therapy to at least 6 months.

INTRODUCTION

For patients with Juvenile Idiopathic Arthritis (JIA) resistant to conventional agents, treatment with biologicals, like etanercept, is a valuable option. Previous studies show 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 three months of treatment for Rheumatoid Arthritis (RA) according to the American College of Rheumatology (ACR) and for both RA and JIA according to the consensus group 2007.[5,6] The British Pediatric Rheumatology Group advises to withdraw biological agents in the event of lack of response after six months of treatment.[7] Due to guidelines and coverage regulations of health insurances in the Netherlands response is evaluated at three months.

Several studies in adults show that a substantial proportion of RA patients who failed to reach the response criteria at three months, and continued treatment, achieved these at six months, indicating a time lag in clinical efficacy.[8-10] JIA patients in whom a delayed response at 6 months was shown are mentioned by Lovell, although no details were given.[11] The objective of our study was to evaluate clinical response of etanercept in JIA patients who failed to meet the response criteria at three months.

MATERIALS AND METHODS

This study is embedded in the Arthritis and Biologicals in Children (ABC)-project, a prospective ongoing multicentre, observational study that includes all Dutch JIA patients using etanercept since the introduction in 1999.[3] Since 2008 a web-based register is used.[12] The study protocol is approved by the Medical Ethics Committee of Erasmus MC, Rotterdam and participating hospitals. In The Netherlands, polyarticular-course JIA patients 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 like phasing out co-medication. In the register, patient and disease characteristics are collected at baseline. Data regarding the course of the disease, 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 or parents, including global assessment of well being by VAS, number of active and limited joints and ESR, are retrieved at start, three months and yearly thereafter. Patients with a follow-up of at least 15 months were selected till November 2008. Response is assessed using the ACR Pediatric 30, 50 and 70 criteria (ACR Pedi 30, 50, 70), defined as at least 30% (resp. 50% and 70%) improvement from baseline in three 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 Wallace.[14]

We defined initial non-responders as patients not achieving ACR Pedi 30 response after three months treatment and secondary responders as initial non-responders who continued treatment, and achieved an ACR Pedi 30 response later during follow-up.

RESULTS

Eligible for inclusion were 179 patients, 70% female, median age at onset JIA 5.8 years (inter-quartile range 3.0-10.0 years) with subtypes summarized in table 10.1.

Table 10.1: 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 (ACR Pedi 30).
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)

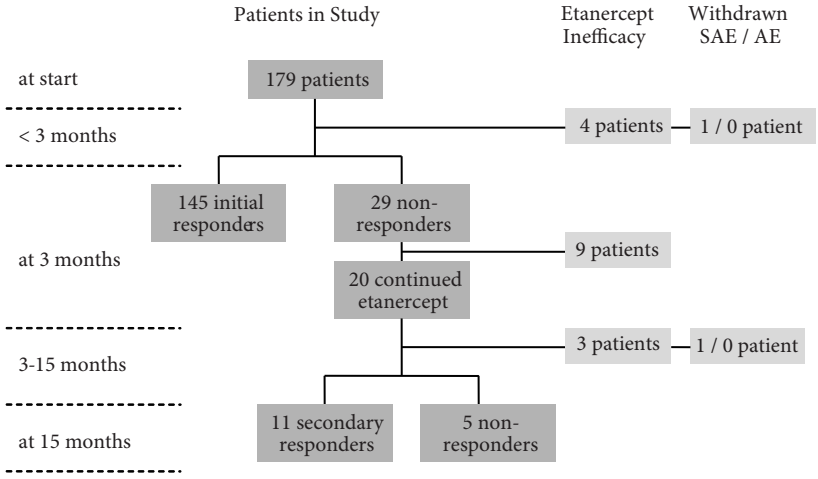

Figure 10.1: Disease course of included patients
SAE, serious adverse event; AE, adverse event

The disease course of the included patients is shown in figure 10.1. Initial non-responders were five patients in whom etanercept was withdrawn before three months of therapy, because of progression of the disease or serious adverse events, and twenty-nine patients who did not meet the ACR Pedi 30 criteria at three 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 ACR Pedi 50 and 73% ACR Pedi 70 response and 36% reached inactive disease at 15 months. None started or raised the dosage of methotrexate or systemic prednisone during etanercept treatment, in the majority co-medication was discontinued (methotrexate in 75% and prednisone in 67% of the patients who used it). Seven percent of all responders are secondary responders.

For the initial 145 responders efficacy analysis according intension to treat results in the following responses at 3 and 15 months: ACR Pedi 30 in respectively 100% and 92%, ACR Pedi 50 in 86% and 90%, ACR Pedi 70 in 66% and 77% and inactive disease in 22% and 38%. Ten patients stopped etanercept between 3 and 15 months due to remission (1), inefficacy (6) or (serious) adverse events (3).

Characteristics of initial responders, secondary responders and non-responders as well as association of initial response with subtypes are shown in table 10.1. The number secondary responders is too small to analyze relations.

DISCUSSION

This study shows that in JIA patients a substantial proportion (55%) of non-responders at three months of treatment, and nevertheless continued etanercept, achieved a response thereafter. In adults this time lag in clinical efficacy is also shown with a 'delayed' response up to 57% at six months in patients that continue treatment despite of insufficient initial response.[8-10]

That the delayed responders achieved relevant improvement is shown by high percentages ACR Pedi 50 and 70 response and even inactive disease in 36%, and by the fact that co-medication has been phased out in the majority of the patients. These results are similar to those of the initial responders at 15 months.

Due to data available in our register, we examined improvement at three 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 moment at six months to our register for a better evaluation. The decision to continue etanercept despite of no ACR Pedi 30 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 three months.

European and American guidelines limit the duration of biological agents in case of no response because of possible (serious) adverse events, unknown long-term effects and high costs, although recently published 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 methotrexate. The increase in response shown in our study is therefore important.

Since in JIA patients a substantial proportion of non-responders at three months who continue etanercept eventually show a clinically relevant improvement, we advise especially in patients with a partial initial response to consider continuation of treatment to at least six months. Recommendations in the current guidelines should be adapted accordingly.

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Part 5

Discussion & Summary

Chapter 11

Discussion and future perspectives

MAIN FINDINGS

- Etanercept is effective in reducing disease activity for a great of the JIA patients (77%) after only three months of therapy (chapter 5).
- This effectiveness is sustained for a longtime; up to 75 months. Of all JIA patients 36% reached disease remission on etanercept (chapter 5).
- Patients with sJIA discontinued etanercept more often due to ineffectiveness, but the same percentage reached remission on the long-term (chapter 5).
- Etanercept has a good safety profile; SAE rate 0.029 per patient year (chapter 5).
- In addition to decreasing disease activity, etanercept can enable a great improvement in health-related quality of life (chapter 6).
- Costs of etanercept are reasonable compared to the health utility gained (chapter 7).
- A once weekly double dose of 0.8 mg/kg is as effective and safe as the usual twice weekly dose of 0.4 mg/kg (chapter 8).
- Etanercept can be discontinued after successful treatment if the patient is in remission according to the Wallace criteria for at least 1.5 years (chapter 9).
- Of all patients who continue etanercept although it was not effective according to the improvement criteria of the ACR Pedi 30 at three months, more than half do respond thereafter (chapter 10).
- A web-based register is an effective and reliable tool to collect data in a multicenter study (chapter 3).
- Digitalization of the Childhood Health Assessment Questionnaire makes complete systematic monitoring of disease activity of JIA patients in daily practice possible (chapter 2).

COMMENTS ON FINDINGS

The main aim of this thesis was to describe the long-term effectiveness and safety of etanercept therapy in Juvenile Idiopathic Arthritis (JIA).

Efficacy and short-term safety of etanercept in JIA was first demonstrated by Lovell et al. in 69 patients in a controlled study.[1] In addition, sustained benefit and safety of etanercept in JIA in an eight years open-label extension study. However, this study group was relatively

small (only 26 patients remained in the study after eight years patients) and the patients already proved to be initially responsive to etanercept before entering the extension study.[1-3] Also, only patients with sJIA, pJIA and oJIA ext were included.

The data from our register proved, in a real-life setting with all Dutch JIA patients using etanercept, the initial but also the sustained effectiveness of etanercept in JIA up to 75 months. This is promising for JIA patients refractory to other second-line agents, including the maximum (tolerated) dose of MTX. However, during steady states of disease remission some patients experiences severe disease flaring. Therefore, we have to conclude that etanercept cannot always completely suppress the disease activity in all JIA patients.

In our study we found that early in treatment effectiveness appeared to be depended on the JIA subtype; in the first three months of treatment more patients with sJIA were unresponsive or less responsive to etanercept than those with other subtypes. Surprisingly, after 15 months of follow-up sJIA patients discontinued etanercept treatment about as frequent as patients from other subtypes. The sJIA patients who responded to etanercept showed the same improvement on the ACR Pedi score after a prolonged time and 38% of all sJIA patients who started etanercept even reached remission on medication. Other studies have reported lower rate of responsiveness of sJIA patients to etanercept. Stated as possible reasons were the severity of disease and other factors such as IL-1 and IL-6 which might play a larger role in sJIA patients than in other subtypes.[4-7] In our study more than half of the sJIA patients was responsive to etanercept (56% improved according to the ACR Pedi 30) after 3 months of therapy. Four out of five systemic JIA who discontinued etanercept because of sustained remission, even retained inactive disease off medication. We therefore argue that etanercept can be very successful in a part of the sJIA patients. A report from the German registry confirms our findings.[8] Studies on other biologicals have not shown a distinctive higher effectiveness in sJIA patients yet.[7,9-12] Possibly, the time to treatment could play an important role. We therefore conclude that it is reasonable to accept etanercept as the first choice in treatment of sJIA patients as long as no new treatments are proven to be more effective.

Etanercept was however more effective in patients from other JIA subtypes in the first three months of treatment; 86% met the improvement criteria of the ACR Pedi 30 in the first three months. In most patients improvement sustained in the following years of therapy, although some patients experienced disease flaring and etanercept was discontinued. Approximately one third of pJIA and oJIA ext patients reached remission. This is inline with data from the German registry.[13]

Although efficacy of etanercept in the subtypes ERA and psJIA, has not been investigated in a randomized controlled trial, we and several other studies have reported on experiences with these patients, indicating good effectiveness and safety.[13-17] Little is known about experiences with etanercept therapy in oJIA pers and uJIA patients, since etanercept is recommended for JIA patients with a polyarticular course.

Other studies have shown the effectiveness of etanercept in JIA on the short-term and long-term.[1,18-22] We summarized the data from all these study in chapter 2. Overall, they confirm our findings.

Our analysis of the outcomes of the JIA core set of six response variables shows that the variable limited joints made the least improvement during follow-up. As Lovell et al. suggested in their study, this is not a quick response variable, and therefore not a good marker for short-term studies.[1] However, some individual patients show major improvements in the number of joints limited in motion.[23] This can most likely be explained by the difference in joints limited in motion by inflammation and joints limited in motion by flex contractures or damage to cartilage or bone.

Management of JIA is complex, especially in children with a severe disease course, and a multidisciplinary approach is often required. Treatment aims for disease remission, meaning controlling inflammation and preventing damage to the joints. There has been a realization in recent years that the impact of musculoskeletal conditions on an individual's life cannot be measured by disease indices such as active joint count, radiographic change and laboratory values alone and that self-reported measures such as pain severity and limitation of daily activity provide important assessments of such conditions.[24] To optimize outcome the effects of treatment should also be evaluated in terms of improvement of quality of life.

We performed the first prospective long-term study on HRQoL changes in JIA patients during etanercept treatment. The results are impressive as they show major improvement of HRQoL in refractory JIA patients during a period of 27 months of etanercept use. The extremely low values before start of etanercept therapy on both the disease specific Childhood Health Assessment Questionnaire as well as the generic Child Health Questionnaire and Health Utility Index Mark 3 indicate the severity of disease activity in these JIA patients, which causes pain, discomfort and deformity of joints. It is of great value to know for these children if a new treatment is likely to be successful in all aspects of health improvement. In general, the outcomes on this study indicate the importance of the introduction of new treatment options for JIA patients refractory to standard care.

During etanercept treatment the extremely low HRQoL levels greatly improved, sometimes even to the same level as in healthy children.[25,26] Outcomes on the CHAQ are reported in most studies on effectiveness of therapy in JIA, however generic questionnaires, such as the CHQ, are not and we were the first to report on the outcomes of the HUI3, although this questionnaire has been validated for pediatric patients.[25-27]

The information on the HRQoL is an important additive on the information from the disease activity score presented in previous studies and is crucial to understand the complete impact of etanercept treatment on JIA patients and their families. Therefore it is advisable to include disease specific and generic HRQoL assessments when evaluating the effectiveness of medication in JIA patients.[28,29]

Although etanercept has been proven to be successful in the treatment of JIA, it also comes with a price, both literally as figurative.

Literally, the costs for etanercept are high compared to more conventional drugs such as MTX. This, of course, has to be seen in the light of the benefits. After start of etanercept therapy total direct medical costs tripled, mainly due to the high cost of etanercept itself. Other direct medical costs, such as costs for consultations and hospitalizations, decreased with 55% during 27 months of etanercept therapy. As stated before, HRQoL measures provide important information on the burden of JIA and the improvements offered by new treatments.[30] Outcomes on the HUI3 indicated a gain of 0.25 in utility (on a scale from 0 to 1) during the use of etanercept. Considering this substantial gain in utility for JIA patients who previously were refractory to conventional treatment and were at risk for long-time disability and pain, costs of etanercept are justifiable. Furthermore, it is expected that early effective treatment of JIA can prevent high costs ongoing throughout adulthood.[30-33] More long-term studies have to be preformed to be able to estimate lifetime utility gain and costs of etanercept.

In a figurative sense the price, in form of occurrence of serious adverse events, seems acceptable. Concerns have been raised about the incidence of malignancies and serious infections.[34] In our national ABC-register no malignancies were reported. However, in the literature nine cases are reported in JIA patients under treatment with etanercept. A study comparing the occurrence in a historical control-group of severely ill JIA patients with the occurrence in JIA patients under etanercept therapy would be helpful. Also more long-term data are needed to fully evaluate the risk of malignancies during etanercept use.

In accordance with previous studies, overall safety of etanercept was demonstrated in our long-term follow-up study, which reports a very low SAE-rate and few AEs.[1-3,7,22,35,36]

Considering the immunosuppressive features of etanercept, opportunistic severe infections are feared. None of the patients in our study developed tuberculosis during etanercept treatment. This is consistent with other studies, which state that the incidence of tuberculosis is lower during etanercept treatment than during infliximab therapy.[37,38] However, two patients developed another granulomatous disease: sarcoidosis. To our knowledge, these are the first cases of sarcoidosis during etanercept therapy yet to be reported. Two patients developed a chronic inflammatory bowel disease (IBD) during etanercept therapy; colitis ulcerosa and Crohn's disease. Although several others cases of new onset IBD during etanercept use were reported, anti-TNF-alpha therapy (mostly infliximab but also etanercept) is described in the literature as a treatment for IBD.[19,22,39-44] This is contradictive and the mechanism behind it is still unknown. More research is required in this field. It has to be taken into account that this was an observational study; only the clinically relevant AEs were reported by the physicians. This might have led to some underreporting compared to controlled clinical trials.

The ACR Pedi 30 criteria are very useful to measure improvements in the research setting, however, physicians are not so much impressed by an ACR Pedi 30 improvement in the daily practice. JIA patients are currently only eligible for biological treatment if they have a polyarticular disease course and refractory to other DMARDs. Therefore, these patients are considered to be severely ill at time of start of the biological. An improvement according to the ACR Pedi 30 is good news for these patients, but the goal of treatment is disease remission. During etanercept treatment approximately half of the patients achieve an ACR Pedi 70 response after only three months and many patients achieve inactive disease and thereafter one third reaches clinical remission on medication. Physicians base their treatment strategies on response to therapy. Ongoing disease activity causes pain and discomfort and may lead to irreversible damage to the joints. In patients in whom disease activity fails to decline on etanercept, physicians are likely to treat these patients more aggressive and raise the dose and concomitant medication. If this fails etanercept is stopped and other therapy options are considered. In addition, physicians want to limit the duration of biological agents in case of no response because of possible (serious) adverse events, unknown long-term effects and high costs, although recently published data on the long-term safety of etanercept show a low rate of serious adverse events.[19-21] We showed in our study that a substantial proportion (55%) of the initial non-responders to etanercept, defined as patients not achieving ACR Pedi 30 response after three months treatment, achieved an ACR Pedi 30 response later during follow-up. That the delayed responders achieved relevant improvement is shown by

high percentages ACR Pedi 50 and 70 response and even inactive disease in 36%, and by the fact that co-medication has been phased out in the majority of the patients. The decision to continue etanercept despite of no ACR Pedi 30 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 signs of improvement at three months. We did not have data at six months of treatment available in the register at the time of the study. The outcomes on this study made us realize the importance of a six months evaluation moment and we therefore added this to the register.

In adults this time lag in clinical efficacy is also shown with a 'delayed' response up to 57% at six months in patients that continue treatment despite of insufficient initial response.[45-47]

Since etanercept is a valuable option for patients previously not responding to other second-line agents, including methotrexate, we advise especially in patients with a partial initial response to continue treatment to at least six months.

Another treatment choice that physicians face is when and how to stop etanercept if treatment has been very successful. Physicians often reduce concomitant medication but act with great caution regarding etanercept treatment, leading to continuation for many years for patients in complete remission. We evaluated 19 JIA patients from the ABC-register who discontinued etanercept because of a sustained good clinical response. Ten of these patients reached inactive disease of medication at the last observation, four even reached clinical remission off medication. Results indicated that patients with a longer remission period according to criteria of clinical remission on medication have a better chance of retaining inactive disease after discontinuation of etanercept. We suggest that JIA patients should meet the criteria of clinical remission on medication for at least 1.5 years before considering discontinuation of etanercept. Another result of this study may be that patients should not discontinue etanercept therapy at once, because it seems to be related with a higher risk of developing a disease flare. This is conform the guidelines from RA treatment.[48] The fact that all eight patients who restarted etanercept after disease flaring regained a good clinical response is reassuring. The characteristics of the disease flares decreased immediately after the restart of etanercept. The study population was too small to show great differences between the JIA subtypes. Findings from this observational study may support clinical decision making and can be the basis for future clinical trails.

Although initially the recommended dose for etanercept in JIA was 0.4 kg/mg SC (maximum 25 mg) twice weekly, studies in RA and a computer based pharmacokinetic model in JIA indicated that a double dose once weekly would be equally effective. We were the first to study the dose of 0.8 mg/kg etanercept in JIA patients. Results from our clinical study support what has been reported in theory in the literature, namely that the once weekly double dose of etanercept is just as effective to retain remission in patients with JIA. Considering the perfect outcome in six patients, in whom etanercept in the double dose once weekly was initiated, it can even induce inactive disease in patients with JIA. There were no SAEs, which confirm the safety of the double dose etanercept. Our results were confirmed by a report from the German register.[49]

One of the big challenges in the project was to keep the national register running. In time, data collection became more difficult because of the rapidly increasing group of patients using etanercept and the increased use of other biologicals. As data accumulate, lack of overview may occur and as a result side-effects of medication and significant events may remain underreported.[50,51] By developing a web-based register we have digitalized the paper case record form and provided an easy and rapid access to the database. An advantage for the user is the possibility to check own data at any given moment and the general data of all participating centres combined. Continuous accurate output and reports has improved the collaboration between the centres and promoted involvement.[51-53] The advantage for the investigator is the continuous access to a complete, up-to-date, multicentre database. In addition, this web-based register has saved the investigator time since data collection has been automated and visits to local centres are reduced. We expect that the use of web-based registers will greatly expand over the next decade and that many collaborative study groups will find it an efficient tool to collect data.

Since we experienced difficulties with systemic monitoring of HRQoL of JIA patients, we decided to digitalize the Childhood Health Assessment Questionnaire (CHAQ) as well. The reliable and user-friendly digital CHAQ can be completed during routine visits at the outpatient clinic in only five minutes and the printed outcome (with automatically calculated scores) is available during the visit.

The majority of the patients and parents preferred the digital CHAQ although it took more time to complete. This is in accordance with results from studies in adults.[54-56] However, because in our study we dealt with paediatric patients and parents, we had to make the digital CHAQ appealing for children as well as adults. We succeeded in this goal since both

patients and parents found the digital version easier to read because of the larger letters and it was more appealing due to the added colours and drawings. Parents of young children experienced more interaction with their child while completing the digital version, which was considered a big advantage. In the future, a touch-screen computer will be used to improve user-friendliness even further. Another option for the future is making the digital CHAQ available online. This way, the patient or parent could already complete the CHAQ at home prior to the hospital visit.

In the future, the digital CHAQ could be connected to the electronic medical records.

There have been several studies in adults on the use of digital health status questionnaires; however our study is the first who reports experiences in a paediatric population.[54,55,57,58] Although only JIA patients were included in our study, the CHAQ can also be applied in children with other chronic musculoskeletal diseases.[59] More generic questionnaires could be used for systematic evaluation of other medical conditions. In general, digitalization of questionnaires can be applied in every field of clinical practice.

In conclusion, this thesis shows that etanercept is effective in reducing disease activity in many Dutch JIA patients, who where previously refractory to treatment with other DMARDs. In addition, it has shown a good long-term safety profile over the last past decade. More long-term safety data are needed and registers hopefully will be able to provide these. In our experience, a web-based register is the most efficient way to manage a multi-center register.

Health-related quality of life improved during therapy and costs of etanercept were acceptable considering the gain in utility.

Use of etanercept was evaluated which resulted in the following recommendations.

Recommended additives to the guidelines:

- Administration of etanercept in the dose of 0.8 mg/kg once weekly as first choice instead of 0.4 mg/kg twice weekly.
- Consider continuation of etanercept if there is a partial response at three months of therapy, even if the improvement of ACR Pedi 30 is not met, up to at least 6 months.
- Consider discontinuation of etanercept if a patient is in clinical remission on medication according to the Wallace criteria for at least 1.5 years.

FUTURE PERSPECTIVES

It is an exciting period in the field of paediatric rheumatology; new insights and therapies are developing rapidly. Despite the lack of a cure, the introduction of etanercept has provided a better quality of life for a lot of JIA patients previously refractory to treatment.

Management of the individual child with JIA will vary with subtype and severity. Outcome seems to improve by better disease control at an early stage; studies on this subject are being performed. Early diagnosis and patient specific treatment will hopefully lead to better outcomes. Learning more about the long-term use of etanercept as well as the pathogenesis of JIA will help to improve treatment. Trials comparing the different biologicals would be ideal. However, large patient groups are needed for these trials and even large collaborative study groups will have difficulties making such studies possible. Registries are also good tools to be able to compare the different outcomes of treatments. It provides valuable information from large patient groups on patient and disease characteristics, disease course and occurrence of adverse events during (multiple) treatment over a long-period of time. In addition, it reflects real-life data from patients as treated by their physician in the clinical setting. To be able to answer research questions, such as long-term safety of biologicals, initiatives have already been made in Europe as well as in the United States of America to combine registries. A large world-wide consolidated JIA registry is the ultimate goal.

Colleagues Ravalli and Martini anticipate that, 10 years from now, classification and treatment of the disease will be revolutionized.[60] Hopefully, the great efforts in the field of paediatric rheumatology research will result in drugs and treatment strategies that are effective and safe for all JIA patients.

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Chapter 12

Summary

PART 1: INTRODUCTION

Background information on this thesis is given in **chapter 1**. Juvenile Idiopathic Arthritis (JIA), formerly known as Juvenile Rheumatoid Arthritis (JRA) or Juvenile Chronic Arthritis (JCA), is the most common cause of chronic arthritis in childhood. The term JIA encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown cause. JIA is a heterogeneous disease comprising several disease subtypes.

Treatment of JIA has in the past relied on nonsteroidal anti-inflammatory drugs (NSAIDs) with slow addition of synthetic disease modifying anti-rheumatic drugs (DMARDS) and thereafter biologicals (biologic DMARDs), with avoidance of systemic glucocorticoids. However, evidence is accumulating that early disease control is important to prevent joint destruction, growth deformities and even blindness (from chronic uveitis associated with JIA). Therefore, JIA therapy has changed in favor of the early introduction of DMARDs and biologicals, occasionally in combination with steroids, with aggressive addition of further agents with a target of disease remission. Since its introduction in 1999 etanercept has become an important treatment option for patients with refractory JIA. It binds to tumour necrosis factor (TNF)-α and TNF-β (lymphotoxin-α) preventing it from interacting with the receptors on the cell surfaces.

This thesis describes the long-term outcomes of etanercept (the most frequently prescribed biological in JIA) treatment in Dutch patients with JIA. In addition, it describes treatment strategies and the methodology of data collection in the 'Arthritis and Biologicals in Children' (ABC) project. This study started in 2003 when the Ministry of Health, Welfare and Sports issued an effectiveness and safety analysis of TNF-α blockers as treatment in JIA. Already prospectively collected data from all JIA patients who used etanercept since 1999, were used for the study, and thereafter new data were collected also prospectively. Since more biologicals became available as (off-label) treatment, the study was extended and was named the ABC-project. Aim is to include all Dutch JIA patients who use or have used a biological in the national register.

Chapter 2 presents an overview of the clinical experiences with etanercept therapy in JIA during the last decade. It discusses what has been reported in the literature on etanercept treatment of JIA until August 2009.

PART 2: METHODS

Chapter 3 describes the development of the web-based ABC-register. Most clinical studies use paper case record forms (CRFs) to collect data. We designed a web-based register with the intention to make it easy to use for participating physicians and at the same time accurate and up-to-date. The web-based register was tested; intern validity was obtained and user-friendliness guaranteed. To secure the completeness of the data automatically generated email alerts were implemented into the web-based register. More transparency of data was achieved by including the option to automatically generate interim reports of data in the web-based register. The safety was tested and approved. By digitalizing the CRF we achieved our aim to provide easy, rapid and safe access to the database and contributed to a new way of data collection.

In **chapter 4** the digitalization of the Childhood Health Assessment Questionnaire (CHAQ), to facilitate systematic monitoring of disease activity at the outpatient clinic in Juvenile Idiopathic Arthritis (JIA) patients, is reported. Validity and user-friendliness were tested with patients who visited the outpatient paediatric rheumatology clinic of the Erasmus MC Sophia Children's Hospital. The majority of patients (75%) preferred the digital version. Such digitalization of questionnaires can be applied in any field to make systematic monitoring of disease activity in daily practice possible.

PART 3: EFFECTIVENESS AND SAFETY

Long-term effectiveness and safety of etanercept are described in **chapter 5**. At baseline data were collected of patient and disease characteristics of all Dutch patients with JIA who started treatment with etanercept till 2007. Disease activity was evaluated (at start of the study, after 3 months and then yearly) according to the JIA core set and the American College of Rheumatology paediatric definition for 30, 50 and 70% improvement (ACR Pedi 30, 50 and 70). Use of etanercept and concomitant drugs was monitored. Adverse events were recorded.

We included 146 patients with JIA with a median follow-up of 2.5 years per patient (range 0.3–7.3). JIA subtypes represented were 27% systemic, 8% polyarticular rheumatoid factor positive, 38% polyarticular rheumatoid factor negative, 19% oligoarticular extended, 3% enthesitis-related and 5% psoriatica. The greatest improvement occurred in the first 3 months

of treatment; patients (77%) met the criteria of the ACR Pedi 30. For the majority of patients this improvement was sustained (up to 75 months) and 53 (36%) of all patients achieved disease remission. No other second-line agents were needed in 43 patients. Although patients with systemic JIA responded initially less to etanercept therapy than patients from other subtypes, the same percentage achieved remission after prolonged treatment. Serious adverse events rate was low (0.029 per patient year). Overall, etanercept was found to be effective and safe for use in the treatment of JIA.

Chapter 6 reports on the changes in Health-Related Quality of Life (HRQoL) in JIA patients during treatment with etanercept. We included 53 JIA patients from seven Dutch centers. HRQoL was measured in these patients at start and after 3, 15 and 27 months of treatment. Major improvements were shown on both the disease specific Childhood Health Assessment Questionnaire (CHAQ) and the generic Child Health Questionnaire (CHQ) and Health Utilities Index mark 3 (HUI3) outcomes. These improvements were already statistically significant after three months and improvements continued at least up to 27 months of treatment. Information from both the disease specific as the generic HRQoL questionnaires is crucial to understand the complete impact of etanercept treatment on JIA patients and their families.

Chapter 7 gives an insight in the costs and effects of etanercept therapy in patients with JIA. Direct medical costs were collected from 49 JIA patients during one-year before and 27 months after start of etanercept and compared to gain in utility according to the Health Utility Index mark 3. Mean total direct medical costs after start etanercept were 12,318 euro per patient per year compared to 3,695 euro before start. Three quarters of costs after start were direct costs of etanercept; other direct medical costs decreased. Utility gain was 0.25 on a scale from 0 to 1. Considering the substantial gain in utility for JIA patients who were previously refractory to conventional treatment and were at risk for long-time disability and pain, costs of etanercept are justifiable.

PART 4: TREATMENT STRATEGIES

In this part of the thesis several treatment strategies are evaluated. In **chapter 8** the dosing strategy of etanercept was tested. Patients with JIA in remission, who prior to the study used etanercept in the usual dose of 0.4 mg/kg SC twice weekly, were switched the double dose of 0.8 mg/kg SC once weekly. After three months, all 11 patients, who were in remission at the start of the study, showed equal values of the response variables compared to start of the study. No flares were seen. In addition, etanercept was initiated in six JIA patients in the once weekly double dose. These patients showed major improvement on the response variables. We showed that the administering of a once weekly double dose of 0.8 mg/kg etanercept is as effective as the twice weekly dose of 0.4 mg/kg to retain remission and induce inactive disease in patients with JIA.

Chapter 9 discusses the issue when and how to stop etanercept after successful treatment of JIA patients. From the patients in the ABC-register, 19 discontinued etanercept because of a sustained good clinical response. For disease course evaluation of these patients we used the Wallace criteria for inactive disease and clinical remission on and off medication. After discontinuation ten patients (53%) had retained remission during a median of 0.8 years. They had used etanercept longer and showed a longer median period of clinical remission on medication compared to the nine patients who flared. We concluded that patients should meet the clinical remission criteria on etanercept for at least 1.5 years before discontinuation. Reassuring was all patients who resumed etanercept use after flaring reacted promptly to treatment.

In **chapter 10** response in JIA patients who failed to meet response criteria at 3 months of etanercept treatment, was evaluated. Responses according to the ACR Paediatric 30 criteria were assessed at start, 3 and 15 months. Of the 179 patients in total, 34 patients did not respond after 3 months, of which 20 continued etanercept and 11 achieved response thereafter. The delayed clinically relevant response in a substantial proportion initially not responding patients justifies continuation of therapy to at least 6 months.

PART 5: DISCUSSION

Etanercept is effective for most JIA patients, who were previously refractory to other DMARDs, including methotrexate. Effectiveness seems to be depended on JIA subtype, although a certain percentage of patients from all subtypes have been successfully treated with etanercept. The safety profile is favorable, but concerns regarding a few SAE on the long-term have been expressed. Impressive was the major improvement in HRQoL, which proves the great impact of etanercept therapy on JIA patients. Costs of etanercept are justifiable in relation to gain in utility.

The web-based register proved to be a very efficient and accurate way of data collection. The digitalization of the CHAQ made complete systemic monitoring of disease activity in JIA patients practical.

Treatment strategies were evaluated which resulted in recommendations for guideline changes; administration of etanercept in the dose of 0.8 mg/kg once weekly, consider continuation of etanercept up to at least 6 months even if the improvement of ACR Pedi 30 is only partial met at three months of therapy, consider discontinuation of etanercept if a patient is in clinical remission on medication according to the Wallace criteria for at least 1.5 years.

Appendices

Nederlandse samenvatting

DEEL 1: INLEIDING

In **hoofdstuk 1** wordt achtergrondinformatie gegeven over dit proefschrift. Juveniele Idiopatische Artritis (JIA), voorheen bekend als Juveniele Reumatoïde Artritis (JRA) of Juveniele Chronische Artritis (JCA), is de meest voorkomende oorzaak van chronische artritis bij kinderen. De term JIA omvat alle vormen van artritis die beginnen voor het 16e levensjaar, langer dan 6 weken aanhouden en waarvan de oorzaak onbekend is. JIA is een heterogene ziekte die onderverdeeld is in verschillende subtypen.

De behandeling van JIA bestond in het verleden voornamelijk uit 'non-steroidal anti-inflammatory drugs' (NSAIDs) met geleidelijke toevoeging van 'synthetische disease modifying anti-rheumatic drugs' (DMARDs) en daarna 'biologicals' (biologische DMARDs), met vermijding van het gebruik van systemische glucocorticoïden. Tegenwoordig zijn er echter steeds meer aanwijzingen zijn dat vroege controle van de ziekte belangrijk is om gewrichtsschade, groeiafwijkingen en zelfs blindheid (door chronische uveïtis geassocieerd met JIA) te voorkomen. Dit heeft geresulteerd in de inzet van DMARDs en biologicals vroeg in de behandeling, al dan niet in combinatie met glucocotricoïden, zonodig met toevoeging van steeds agressiever middelen met als doel de ziekte in remissie te krijgen.

Etanercept is, sinds het geregistreerd werd in 1999, een belangrijke behandelingsoptie geworden voor patiënten met moeilijk behandelbare JIA. Het bindt aan Tumour Necrosis Factor (TNF)-α and TNF-β (lymphotoxin-α) en voorkomt daardoor een interactie met de receptoren op de celoppervlakken.

Dit proefschrift beschrijft de lange termijn uitkomsten van de behandeling van Nederlandse JIA patiënten met etanercept, de meest voorgeschreven biological voor JIA patiënten. Daarnaast beschrijft het ook behandelingsstrategieën en de methodologie van dataverzameling in het 'Arthritis and Biologicals in Children' (ABC) project. Deze studie startte in 2003 toen het Ministerie van Gezondheid, Welzijn en Sport opdracht gaf tot het uitvoeren van een studie naar inzet, effectiviteit en veiligheid van TNF-α blokkers in de behandeling van JIA. Reeds prospectief verzamelde data van alle JIA patiënten die gestart waren met etanercept vanaf 1999 werden gebruikt en nieuwe gegevens werden vervolgens tevens prospectief verzameld. Toen er in de afgelopen jaren meer biologicals beschikbaar

kwamen voor de (off-label) behandeling van JIA, werd de studie uitgebreid en benoemd tot het ABC-project. Het doel is om alle Nederlandse kinderen die een biological gebruiken te includeren en te volgen in het nationale ABC-register.

Hoofdstuk 2 geeft een overzicht van de klinische ervaringen met etanercept in de behandeling van JIA gedurende het laatste decennium. Er wordt bediscussieerd wat gerapporteerd werd in de wetenschappelijke literatuur over de behandeling van JIA patiënten met etanercept tot en met augustus 2009.

DEEL 2: METHODE

Hoofdstuk 3 beschrijft de ontwikkeling van het web-based ABC-register. De meeste klinische studies gebruiken case record forms (CRFs) om op papier data te verzamelen. Wij hebben een web-based register ontworpen met de intentie het gebruiksvriendelijk te maken voor de deelnemende artsen en tegelijkertijd accuraat en up-to-date. Het web-based register werd getest; zowel interne validiteit als gebruiksvriendelijkheid werden goedgekeurd. De mogelijkheid tot het verzenden van automatisch gegenereerde emails werd geïmplementeerd in het web-based register om compleetheid van data te bevorderen. Door een optie te geven in het web-based register om automatische gegenereerde interim rapporten te creëren, werden data transparanter. De veiligheid werd grondig getest en bevestigd. Door het digitaliseren van de CRF hebben we ons doel bereikt om een makkelijke, snelle en veilige toegang tot de database te realiseren en hebben we bijgedragen aan een nieuwe manier van dataverzameling.

In **hoofdstuk 4** wordt de digitalisatie van de Childhood Health Assessment Questionnaire (CHAQ), om te voorzien in systematische montoring van ziekteactiviteit bij JIA patiënten op de polikliniek, gerapporteerd. Validiteit en gebruiksvriendelijkheid werden getest met patiënten die de polikliniek kinderreumatologie in het Erasmus MC Sophia Kinderziekenhuis bezochten. De meerderheid van de patiënten (75%) gaven de voorkeur aan de digitale versie. Een dergelijke digitalisering van vragenlijsten kan in elk deelgebied van de geneeskunde systematische monitoring van ziekteactiviteit bij patiënten in de dagelijkse praktijk mogelijk maken.

DEEL 3: EFFECTIVITEIT EN VEILIGHEID

De lange termijn effectiviteit en veiligheid van etanercept zijn beschreven in **hoofdstuk 5**. Bij start van etanercept werden patiënten- en ziektekarakteristieken verzameld van alle Nederlandse patiënten met JIA die startten met etanercept tot 2007. Ziekteactiviteit werd geëvalueerd, met behulp van de 'JIA core set', bij start van de studie, na 3 maanden en vervolgens jaarlijks. Verbetering van de ziekteactiviteit werd beschreven volgens de definitie van de 'American College of Rheumatology Pediatric', waarbij werd bepaald of er sprake was van tenminste een 30, 50 of 70% verbetering (ACR Pedi 30, 50 en 70) op de verschillende variabelen van de JIA core set. Gebruik van etanercept en co-medicatie werd bijgehouden. Bijwerkingen werden genoteerd.

In totaal includeerden we 146 JIA patiënten met een mediane follow-up duur van 2.5 jaar per patiënt (range 0.3–7.3). Verdeling in JIA subtypes was 27% systemisch, 8% polyarticulair reumafactor positief, 38% polyarticulair reumafactor negatief, 19% oligoarticulair uitgebreid, 3% enthesitis gerelateerd en 5% psoriatica. De grootste verbetering vond plaats tijdens de eerste drie maanden van behandeling; 77% van de patiënten voldeed aan de criteria van de ACR Pedi 30. In de meerderheid van de patiënten bleef deze verbetering bestaan (tot aan 27 maanden) en in 53 (36%) van alle patiënten werd remissie van de ziekte bereikt. Geen andere DMARDs waren nodig voor behandeling bij 43 patiënten. Hoewel patiënten met systemische JIA initieel minder goed respondeerden op etanercept therapie dan patiënten van andere subtypen, werd uiteindelijk in hetzelfde percentage remissie van de ziekte bereikt na langdurig behandeling. Er werden weinig ernstige bijwerkingen gemeld (0.029 per patiëntenjaar). Over het geheel werd geconcludeerd dat etanercept effectief en veilig is voor langdurige behandeling van JIA.

Hoofdstuk 6 rapporteert de veranderingen in gezondheid gerelateerde kwaliteit van leven; 'Health-Related Quality of Life' (HRQoL), bij JIA patiënten gedurende behandeling met etanercept. We includeerden 53 JIA patiënten vanuit zeven Nederlandse centra. HRQoL in deze patiënten werd gemeten bij start en na 3, 15 en 27 maanden behandeling. Enorme verbeteringen werden gezien op de uitkomsten van zowel het ziektespecifieke meetinstrument 'Childhood Health Assessment Questionnaire' (CHAQ) als de generieke meetinstrumenten 'Child Health Questionnaire' (CHQ) en 'Health Utilities Index mark 3' (HUI3). Deze verbeteringen waren al statistische significant na 3 maanden en bleven voortduren tot 27 maanden behandeling. Informatie van zowel ziektespecifieke als generieke vragenlijsten zijn cruciaal om de volledige impact van de behandeling met etanercept op de JIA patiënten en hun families te begrijpen.

Hoofdstuk 7 geeft inzicht in de kosten en effecten van etanercept therapie in JIA patiënten. Van 49 JIA patiënten werden de direct medische kosten verzameld gedurende één jaar voor en 27 maanden na start van etanercept en dit werd vergeleken met verbetering in utiliteit volgens het meetinstrument HUI3. Totale directe medische kosten na start etanercept waren gemiddeld 12,318 euro per patiënt per jaar tegenover 3,695 euro voor start. Driekwart van de kosten na start waren direct afkomstig van etanercept zelf, de andere direct medische kosten daalden. Winst in utiliteit was 0.25 (op een schaal van 0 tot 1). Gezien de geweldige verbetering in utiliteit voor JIA patiënten die voorheen niet reageerde op therapieën met als gevaar langdurige invaliditeit en pijn, zijn de kosten van etanercept te rechtvaarden.

DEEL 4: BEHANDELINGSSTRATEGIEËN

In dit deel van het proefschrift worden de verschillende behandelingsstrategieën geëvalueerd. In **hoofdstuk 8** wordt de doseringsstrategie van etanercept getest. Patiënten met JIA in remissie, die voor de studie de gebruikelijke dosis van 0.4 mg/kg subcutaan (SC) twee keer per week kregen, werden omgezet naar de dubbele dosis van 0.8 mg/kg SC één keer per week. Bij alle 11 patiënten, die in remissie waren bij start van de studie, werden na drie maanden dezelfde waarden gezien op de response variabelen als aan het begin van de studie. Er waren geen ziekteopvlammingen. Daarnaast werd etanercept ook nieuw gestart in de dosis van 0.8 mg/kg één keer per week in zes patiënten met JIA. Deze patiënten lieten uitstekende verbeteringen zien op de response variabelen. We hebben daarmee aangetoond dat etanercept in de dosering van 0.8 mg/kg één keer per week net zo effectief is als de dosering van 0.4 mg/kg twee keer per week voor het behouden van remissie en het induceren van inactieve ziekte in patiënten met JIA.

Hoofdstuk 9 bespreekt de kwestie wanneer en hoe er gestopt kan worden met etanercept na succesvolle behandeling van JIA patiënten. Van alle patiënten in het ABC-register stopten 19 wegens een langdurige goede klinische respons. Om het verloop van de ziekte objectief te evalueren gebruikten we de criteria van Wallace voor inactieve ziekte en klinische remissie, met en zonder medicatie. Na het discontinueren van etanercept behielden tien patiënten (53%) remissie gedurende 0.8 jaar (mediaan). Zij gebruikten etanercept langer en hadden een langere periode van klinische remissie met medicatie vergeleken met de negen patiënten die een opvlamming van JIA kregen. We concludeerden dat de patiënten tenminste 1.5 jaar zouden

moeten voldoen aan de criteria voor klinische remissie op etanercept voordat er gestopt wordt met behandeling. Geruststellend was dat alle patiënten die een ziekteopvlamming kregen goed reageerden op herstart van etanercept.

In **Hoofdstuk 10** wordt de respons in JIA patiënten die niet voldeden aan de respons criteria na 3 maanden behandeling met etanercept geëvalueerd. Respons volgens de ACR Pedi 30 criteria werd bepaald voor start en na 3 en 15 maanden therapie. Van de 179 patiënten in totaal, respondeerden 34 patiënten niet na 3 maanden. Daarvan continueerden 20 patiënten etanercept en behaalde 11 alsnog een goede respons. De vertraagde maar relevante klinische respons bij een substantieel deel van de patiënten die initieel niet reageerde, rechtvaardigt continuering van etanercept tot tenminste 6 maanden.

DEEL 5: DISCUSSIE

Etanercept is effectief in de behandeling van het grootste deel van JIA patiënten die voorheen niet reageerden op andere DMARDS, inclusief methotrexaat. Effectiviteit lijkt deels afhankelijk te zijn van JIA subtype, hoewel een groot percentage patiënten van elk subtype goed reageert op behandeling met etanercept. Het veiligheidsprofiel van etanercept is gunstig aangezien er weinig ernstige bijwerkingen werden gemeld gedurende de studie, maar de enkele ernstige bijwerkingen die voorkwamen zorgen wel voor enige ongerustheid. Daarom is het belangrijk om onderzoek te blijven doen naar de lange termijn veiligheid. De verbetering in HRQoL tijdens etanercept therapie was indrukwekkend. Dit laat zien dat de behandeling met etanercept een enorme positieve invloed heeft op de kwaliteit van leven van kinderen met JIA.

Het web-based register heeft bewezen een zeer efficiënte en accurate manier van dataverzameling te zijn. Het digitaliseren van de CHAQ heeft het mogelijk gemaakt om ziekteactiviteit in JIA patiënten compleet bij te houden in de dagelijkse praktijk.

Behandelingstrategiën werden geëvalueerd wat resulteerden in de volgende aanbevelingen voor nieuwe richtlijnen; toediening van etanercept in de dosering van 0.8 mg/kg één keer per week, overweging continueren van de behandeling met etanercept tot tenminste zes maanden in het geval van slechts een gedeeltelijke respons bij drie maanden therapie, overweging stoppen van de behandeling in het geval dat de patiënt minimaal 1.5 jaar in klinische remissie op medicatie is volgens de criteria van Wallace.

Dankwoord

"As we express our gratitude, we must never forget that the highest appreciation is not to utter words, but to live by them" ***John F. Kennedy***

Allereerst veel dank aan degene zonder wie deze scriptie er absoluut nooit gekomen was, mijn co-promoter Dr. Lisette W.A. van Suijlekom-Smit. Lisette is enorm gedreven, met veel passie voor haar werk en 1001 goede ideeën. Ik had geen bedenktijd nodig toen de vraag kwam of ik bij haar promotieonderzoek wilde doen. Ik ben haar enorm dankbaar voor al die deuren die ze voor mij geopend heeft. Ik had mij geen betere co-promotor kunnen wensen.

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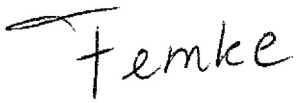

Curriculum Vitae

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2008-2009	Board of the paediatric researchers association Sophia Children's Hospital
2007-2009	Resident at the paediatric emergency department of the Erasmus MC Sophia Children's Hospital (half day per week)
2003-2005	Organization of health conventions at University Maastricht (part time)
2002-2003	Board of student association "Maastrichtse Studenten Vereniging Tragos" (full time)

Research project

2006-present	National study on Arthritis and Biologicals in Children (ABC-project), department of paediatrics and paediatric rheumatology, Erasmus MC Sophia Children's Hospital, project leader L.W.A. van Suijlekom-Smit, MD, PhD

Courses and conventions

- Combined European Congress of Rheumatology (EULAR) and Pediatric Rheumatology Congress (PReS) Copenhagen, 10-13 June 2009
- Young Investigators Meeting 16th PReS Congress, Copenhagen, 9 June 2009
- Public Workshop Developing a Consolidated Pediatric Rheumatology Observational Registry, FDA, Silver Spring, 12-13 May 2009
- Annual Paediatric Research Day Sophia Children's Hospital, 18 December 2008
- Young Investigator Day; Dutch Association for Paediatrics, Veldhoven, 4 November 2008
- Young Investigators Meeting 15th PReS Congress, London, 13 September 2008
- 15th European Paediatric Rheumatology Congress (PReS) London, 14-17 September 2008
- Course "Integrity in medical research", department of Medical Ethics and Philosophy Faculty of Medicine and Health Care, Erasmus MC, June and July 2008
- Annual European Congress of Rheumatology, EULAR, Paris, 11-14 June 2008
- 11th Congress of the European Society for Development, Perinatal and Paediatric Pharmacology (ESDP), Rotterdam, 4-7 June 2008

- Young Investigator Day; Dutch Association for Paediatrics, Veldhoven, 8 October 2007
- Congress Women In Science Education Research (WISER); NWO, Maastricht, 5 October 2007
- Young Investigators Meeting 14th PReS Congress, Istanbul, 5 September 2007
- 14th European Paediatric Rheumatology Congress (PReS) Istanbul, 6-9 September 2007
- Course "Biomedical English Writing and Communication", Erasmus MC, March until July 2007
- Symposium "Beyond the evidence; Cochrane's reflections on evidence based medicine", Dutch Cochrane Centre, University of Amsterdam, 18 April 2007
- Course "Methodology of research in patients and tips on application for research grants", Erasmus MC, 13 February 2007
- Course "Good Clinical Practice", Erasmus Winter Programme, NIHES, 22-26 January 2007
- Course "Analyse and publish medical scientific research", Postgrade, prof. K.G.M. Moons, PhD, Zeist, 16 November 2006
- Course "Write a scientific article and get it published", Postgrade, Tim Albert, Zeist, 11 October en 15 November 2006

Invited lecture

Femke H.M. Prince. Ins and outs of a web-based national register. *Public Workshop Developing a Consolidated Pediatric Rheumatology Observational Registry, FDA, Silver Spring, 12-13 May 2009*

Abstracts en presentations

Femke H.M. Prince, Lianne M. Geerdink, Gerard J.J.M. Borsboom, Marinka Twilt et al. Major improvements in Health-Related Quality of Life during the use of etanercept in patients with refractory Juvenile Idiopathic Arthritis *Combined European Congress of Rheumatology (EULAR) and Pediatric Rheumatology Congress (PReS) London, 10-13 June 2009* [oral (to international press) and poster presentation]

Femke H.M. Prince, Lianne M. Geerdink, Gerard J.J.M. Borsboom, Marinka Twilt et al. Major improvements in Health-Related Quality of Life during the use of etanercept in patients with refractory Juvenile Idiopathic Arthritis *Young Investigators Meeting 16th European Pediatric Rheumatology Congress (PReS) Copenhagen, 9 June 2009* [poster presentation]

Femke H.M. Prince, Lianne M. Geerdink, Gerard J.J.M. Borsboom, Marinka Twilt et al. Major improvements in Health-Related Quality of Life during the use of etanercept in patients with refractory Juvenile Idiopathic Arthritis. *Annual Paediatric Research Day Sophia Children's Hospital, 18 December 2008* [oral presentation]

F.H.M. Prince, I.S. Ferket, S.S.M. Kamphuis, W. Armbrust et al. Development of a web-based register for the Dutch national study on biologicals in JIA: www.ABC-register.nl *Young Investigator Day; Dutch Association for Paediatrics, Veldhoven, 4 November 2008* [poster presentation]

F.H.M. Prince, M. Twilt, S.C.M. Simon, M.A.J. van Rossum et al. When and how to stop etanercept after successful treatment of patients with Juvenile Idiopathic Arthritis. *15th European Pediatric Rheumatology Congress (PReS) London, 14-17 September 2008* [poster presentation]

F.H.M. Prince, I.S. Ferket, S.S.M. Kamphuis, W. Armbrust et al. Development of a web-based register for the Dutch national study on biologicals in JIA: www.ABC-register.nl. *15th European Pediatric Rheumatology Congress (PReS) London, 14-17 September 2008* [poster presentation]

F.H.M. Prince, M. Twilt, S.C.M. Simon, M.A.J. van Rossum et al. When and how to stop etanercept after successful treatment of patients with Juvenile Idiopathic Arthritis. *Young Investigators Meeting 15th European Pediatric Rheumatology Congress (PReS) London, 13 September 2008* [poster presentation]

F.H.M. Prince, I.S. Ferket, S.S.M. Kamphuis, W. Armbrust et al. Development of a web-based register for the Dutch national study on biologicals in JIA: www.ABC-register.nl. *Young Investigators Meeting 15th European Pediatric Rheumatology Congress (PReS) London, 13 September 2008* [poster presentation]

F.H.M. Prince, I.S. Ferket, S.S.M. Kamphuis, W. Armbrust et al. Development of a web-based register for the Dutch national study on biologicals in JIA: www.ABC-register.nl. *Annual European Congress of Rheumatology, EULAR, Paris, 11-14 June 2008* [poster presentation]

F.H.M. Prince, I.S. Ferket, S.S.M. Kamphuis, W. Armbrust et al. Development of a web-based register for the Dutch national study on biologicals in JIA: www.ABC-register.nl. *11th Congress of the ESDP, Rotterdam, 4-7 June 2008* [poster presentation]

F.H.M. Prince, M. Twilt, R. Ten Cate, M.A.J. van Rossum et al. Long-term follow-up on effectiveness and safety of etanercept in JIA: the Dutch national register. *11th Congress of the ESDP, Rotterdam, 4-7 June 2008* [poster presentation]

F.H.M. Prince, M. Twilt, R. Ten Cate, M.A.J. van Rossum et al. Long-term follow-up on effectiveness and safety of etanercept in JIA: the Dutch national register. *Young investigators day; Dutch Association of Peadiatrics, Veldhoven, 8 October 2007* [poster presentation]

F.H.M. Prince, L.W.A. van Suijlekom-Smit. Also children deserve good drug research. *WISER, Maastricht, 5 October 2007* [oral presentation]

F.H.M. Prince, M.Twilt, C.J.A. Jansen-Wijngaarden, L.W.A. van Suijlekom-Smit.
Once weekly double dose etanercept is as effective as twice weekly usual dose in retaining and inducing remission in JIA. *Young Investigators Meeting 14th PReS Congress, Istanbul, 5 September 2007* [poster presentation]

F.H.M. Prince, M.Twilt, C.J.A. Jansen-Wijngaarden, L.W.A. van Suijlekom-Smit.
Once weekly double dose etanercept is as effective as twice weekly usual dose in retaining and inducing remission in JIA. *14th European Pediatric Rheumatology Congress (PReS) Istanbul, 6-9 September 2007* [poster presentation]

F.H.M. Prince, M.Twilt, C.J.A. Jansen-Wijngaarden, L.W.A. van Suijlekom-Smit. Effectiveness of a once weekly double dose of etanercept in patients with JIA: a clinical study. *Annual European Congress of Rheumatology (EULAR 2007), Barcelona 2007* [poster presentation]

List of publications

M.H. Otten, **F.H.M. Prince**, M. Twilt, M.A.J. van Rossum, W. Armbrust, E.P.A.H. Hoppenreijs, S.S.M. Kamphuis, Y. Koopman-Keemink, N.M. Wulffraat, S.L. Gorter, R. ten Cate, L.W.A. van Suijlekom-Smit. Delayed clinical response in patients with Juvenile Idiopathic Arthritis treated with etanercept. Accepted for publication (The Journal of Rheumatology).

F.H.M. Prince, L.M. Geerdink, G.J.J.M. Borsboom, M. Twilt, M.A.J. van Rossum, E.P.A.H. Hoppenreijs, R. ten Cate, Y. Koopman-Keemink, M. van Santen-Hoeufft, H. Raat , L.W.A. van Suijlekom-Smit. Major improvements in Health-Related Quality of Life during the use of etanercept in patients with previously refractory Juvenile Idiopathic Arthritis. Ann Rheum Dis. 2009 (epub ahead of print).

L.M. Geerdink, **F.H.M. Prince**, C.W.N. Looman, L.W.A. van Suijlekom-Smit. Development of a digital Childhood Health Assessment Questionnaire for systematic monitoring of disease activity in daily practice. Rheumatology (Oxford). 2009;48(8):958-63.

F.H.M. Prince, M. Twilt, S.C.M. Simon, M.A.J. van Rossum, W. Armbrust, E.P.A.H. Hoppenreijs, S.S.M. Kamphuis, M. van Santen-Hoeufft, Y. Koopman-Keemink, N.M. Wulffraat, R. ten Cate, L.W.A. van Suijlekom-Smit When and how to stop etanercept after successful treatment of patients with Juvenile Idiopathic Arthritis. Ann Rheum Dis. 2009;68(7):1228-9.

F.H.M. Prince, M. Twilt, R. ten Cate, M.A.J. van Rossum, W. Armbrust, E.P.A.H. Hoppenreijs, M. van Santen-Hoeufft, Y. Koopman-Keemink, N.M. Wulffraat, L.W.A. van Suijlekom-Smit. Long-term follow-up on effectiveness and safety of etanercept in Juvenile Idiopathic Arthritis: the Dutch national register. Ann Rheum Dis. 2009;68(5):635-41.

F.H.M. Prince, I.S. Ferket, S. Kamphuis, W. Armbrust, R. ten Cate, E.P.A.H. Hoppenreijs, Y. Koopman-Keemink, M.A.J. van Rossum, M. van Santen-Hoeufft, M. Twilt, L.W.A. van Suijlekom-Smit. Development of a web-based register for the Dutch national study on biologicals in JIA: www.ABC-register.nl. Rheumatology (Oxford). 2008;47(9):1413-6.

F.H.M. Prince, L.W.A. van Suijlekom-Smit. Initiating etanercept in a once weekly dose in children with Juvenile Idiopathic Arthritis. Rheumatol Int 2008;28(4):397-8

F.H.M. Prince, M. Twilt, C.J.A. Jansen-Wijngaarden, L.W.A. van Suijlekom-Smit. Effectiveness of a once weekly double dose of etanercept in patients with JIA: a clinical study. Ann Rheum Dis. 2007;66(5):704-5.

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Color figures

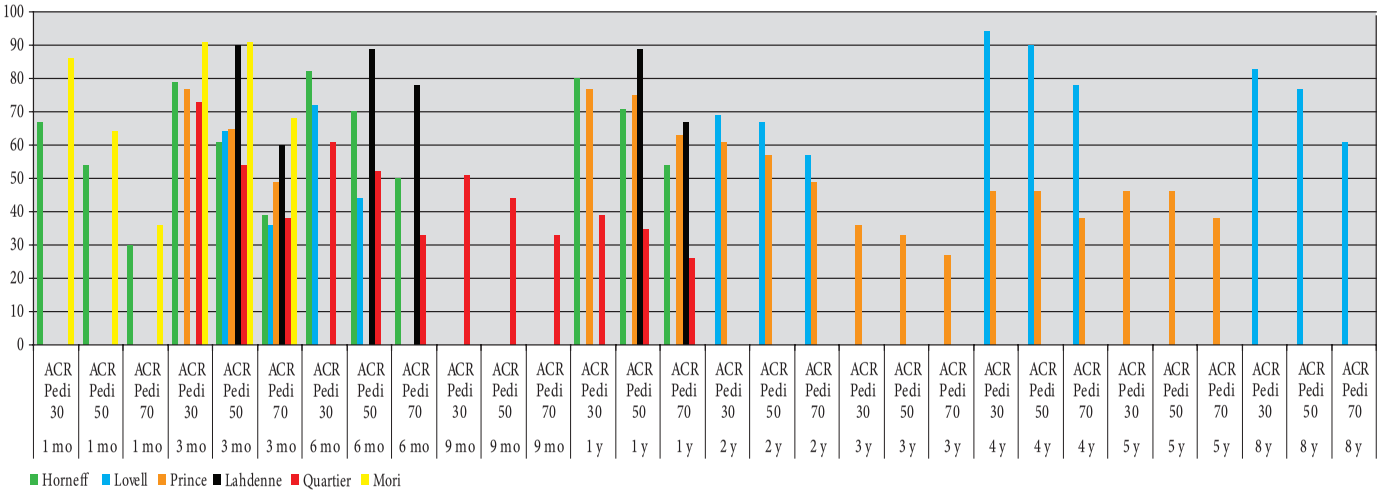


Figure 2.1: ACR Pedi 30, 50 and 70 improvements (see page 38)

Horneff (43); based on last observation carried forward (LOCF)

Lovell (13, 48-50); based on LOCF

Prince (27); based on intention to treat analysis (ITT)

Lahdenne (46); based on ITT analysis (only 10 patients included)

Quartier (21); based on ITT analysis

Mori (51); all 22 patients were included in the analysis,

Mo; months, Y; years

Chapter 3

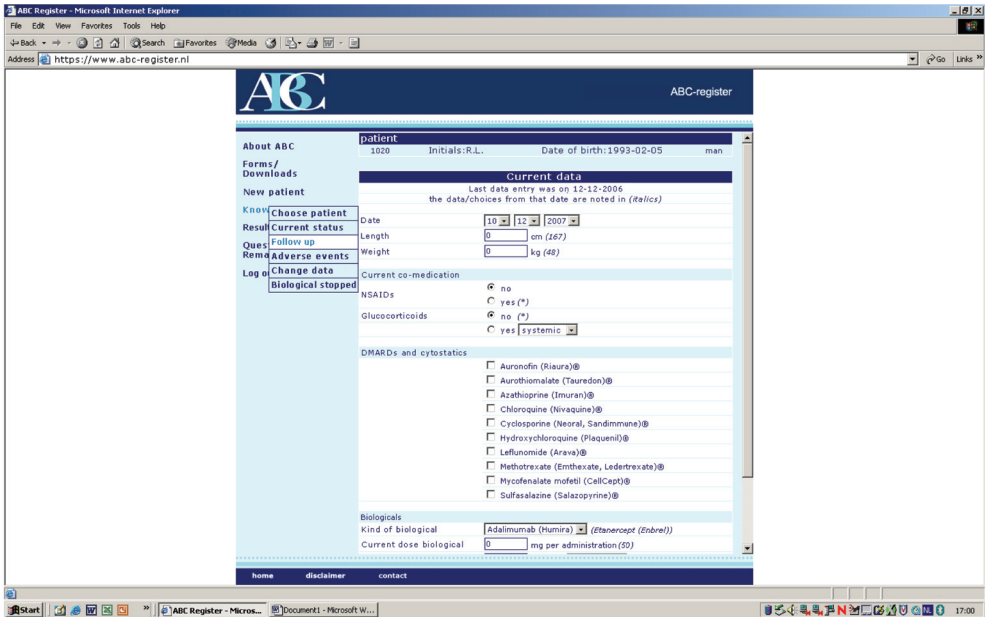


Figure 3.1: Screenshot 1 (translated into English for publication) (see page 72). Entering and retrieving data; the upper left side of the screen shows the menu, in which the user can choose the options 'About ABC', 'Forms/ Downloads', 'New patient', 'Known patient', 'Results', 'Questions/ Remarks' or 'Log out'. The right side of the screen displays an entry form for follow-up data. The imported data from the last follow-up for this patient are shown in brackets and italic font style on the screen as a reminder for the user.

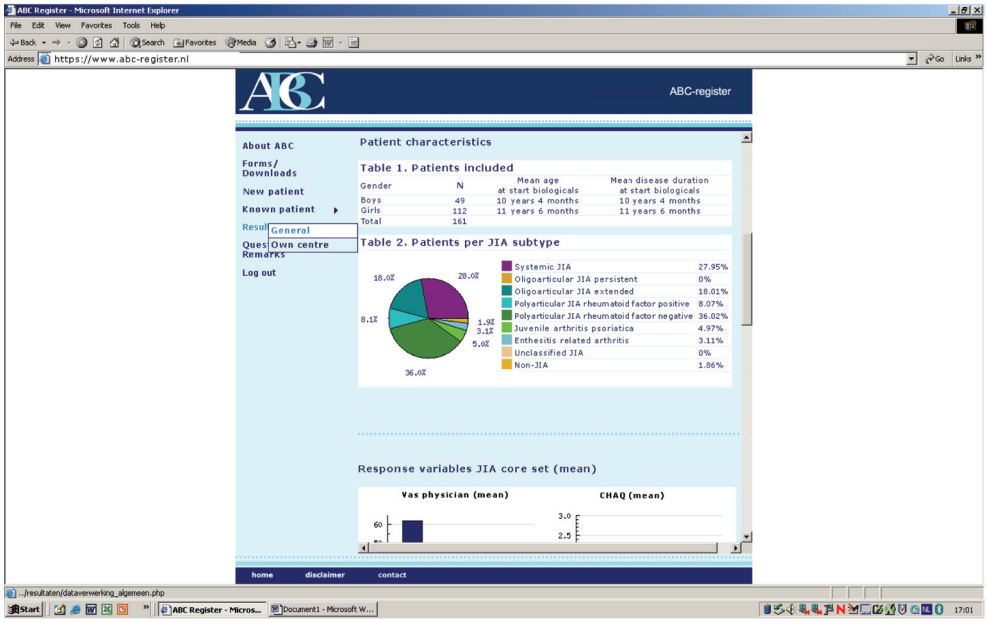
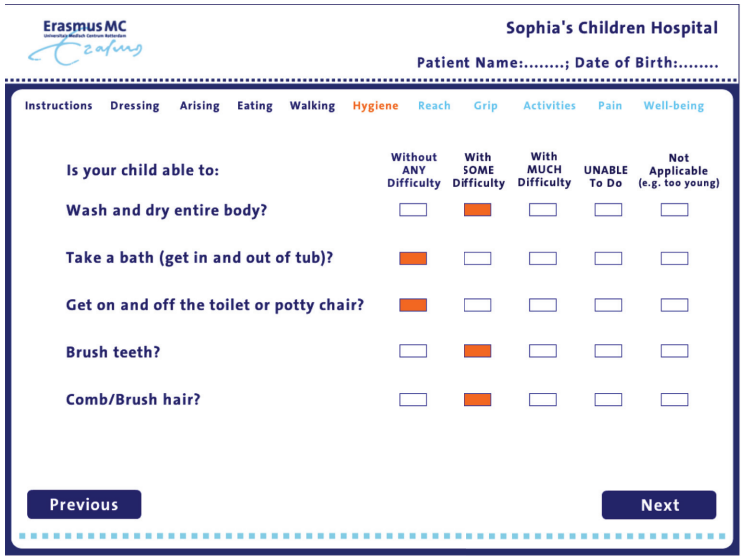


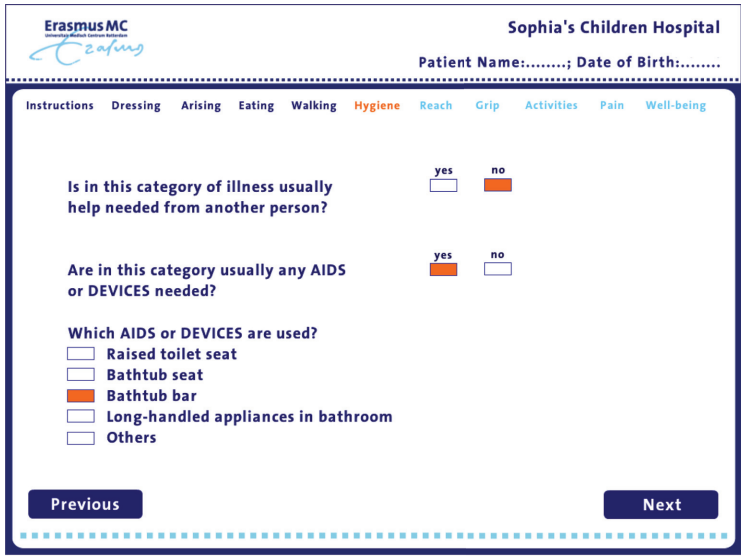
Figure 3.2: Screenshot 2 (translated into English for publication) (see page 73). Reports; an example of an interim report of the combined imported data from all the participating centres. This part shows the patients included by gender, the mean age and the mean disease duration at start of the biological (Table 1) and the percentages of JIA subtypes included (Table 2).

Chapter 4

Figure 4.1: Examples of screens of the digital CHAQ (translated in English for publication) (see page 84). **Screenshot A; Domain 'Hygiene' is announced**



Screenshot B; The five items of the domain 'Hygiene' are completed



Screenshot C; The use of aids or devices in the domain 'Hygiene' is evaluated

Chapter 6

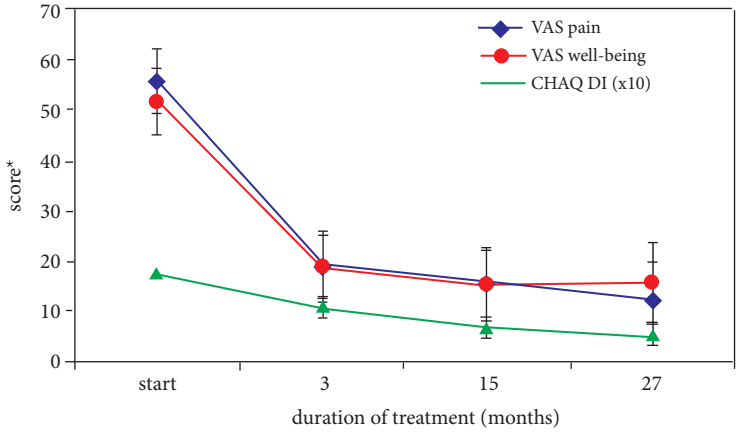


Figure 6.1: Childhood Health Assessment Questionnaire (CHAQ) (see page 123)**;**
Changes in mean outcomes during treatment with etanercept of the CHAQ DI, VAS pain and VAS well-being within 95% confidence limits (+/- 1.96*standard error of the mean).
CHAQ DI (x10): Childhood Health Assessment Questionnaire Disability Index score (range 0-3) multiplied by ten; VAS: Visual Analogue Scale (range 0-100)
*Change over time: CHAQ DI $p < 0.001$, VAS pain $p < 0.001$, VAS well-being $p < 0.001$

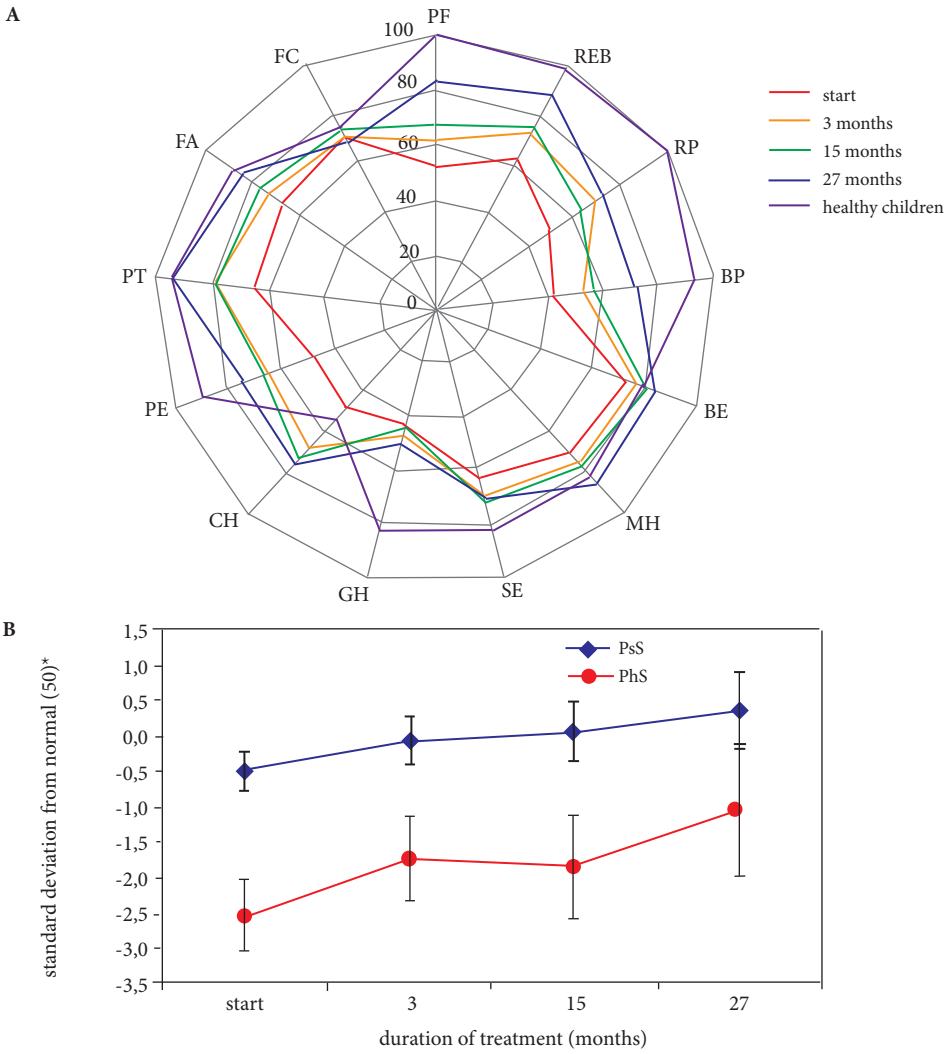


Figure 6.2 A and B: Child Health Questionnaire (CHQ) (see page 126)**.**
Changes in mean outcomes during treatment with etanercept in all health concepts (A) compared to the outcomes in healthy children.[22] Changes in the PhS and PsS summary scores (B) within 95% confidence limits (+/- 1.96*standard error of the mean). The PhS and PsS summary scores are expressed in standard deviation from the normal mean value of 50.[22] PF: Physical functioning; REB: role functioning: emotional/behavioural limitations, RP: role functioning: physical limitations; BP: bodily pain/discomfort; BE: general behaviour perception; MH: mental health; SE: self-esteem; GH: general health perceptions; CH: change in health; PE: emotional impact on the parent; PT: impact on the

parent's personal time; FA: limitations on family activities and FC: family cohesion. PhS: Physical summary Scale; PsS: Psychosocial summary Scale. *Change over time: PhS p = 0.005, PsS p = 0.004

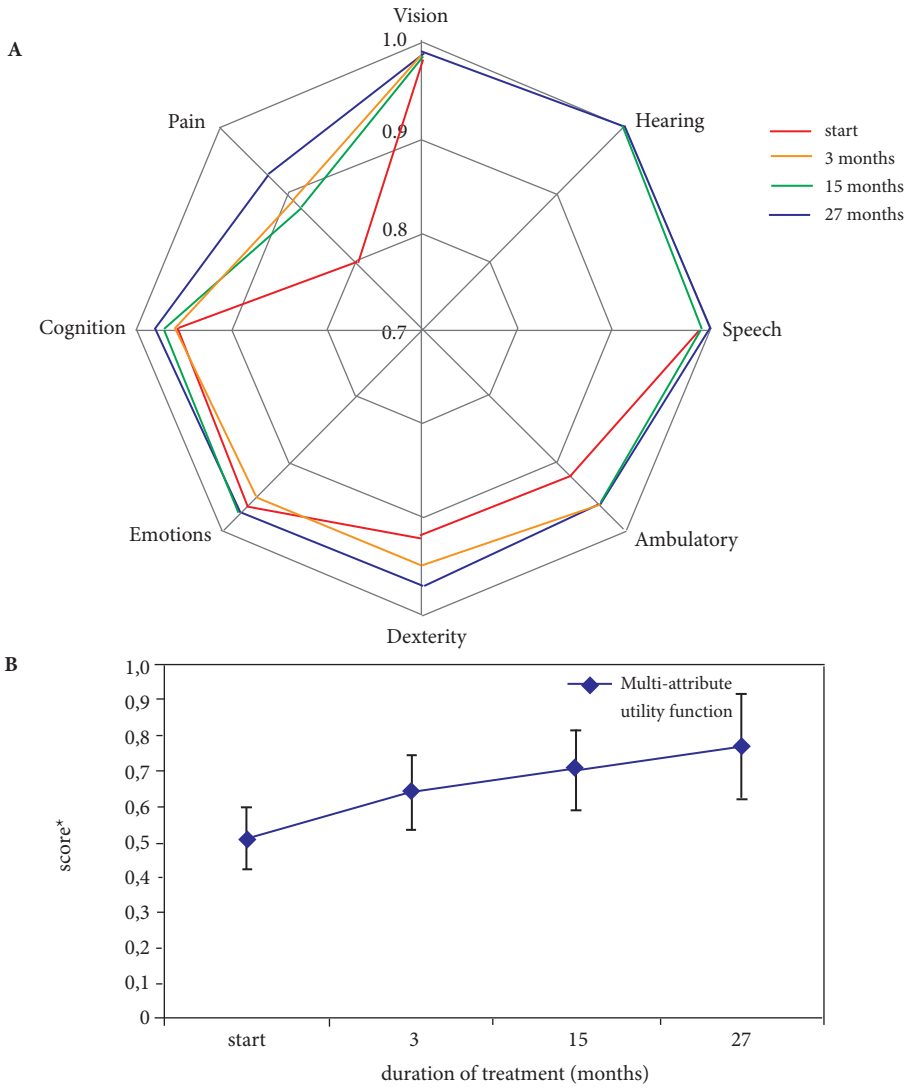


Figure 6.3 A and B: Health Utilities Index Mark 3 (HUI3) (see page 127)**.**
Changes during treatment with etanercept in the mean single (A) and multi-attribute utility (B) function scores (range 0-1) on a death-health scale within 95% confidence limits (+/- 1.96*standard error of the mean). *Change over time: multi-attribute utility function p=0.001