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Disease Modifying Drug Treatment
in Juvenile Idiopathic Arthritis



ACADEMIC DISSERTATION

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List of original papers

This thesis is based on the following original publications, which will be referred to their Roman numerals:

I Haapasaari J, Kautiainen H, Hakala M. Combining cyclosporine with prevailing antirheumatic drug therapy in the treatment of juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002;20: 259

II Haapasaari J, Kautiainen H, Isomäki H, Hakala M. Hydroxychloroquine does not decrease serum methotrexate concentration in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;52:1621-2

III Lahdenne P, Rapola J, Ylijoki H, Haapasaari J. Hepatotoxicity in patients with juvenile idiopathic arthritis receiving longterm methotrexate therapy. *J Rheumatol* 2002;29: 2442-5

IV Haapasaari J, Kautiainen H, Hannula S, Pohjankoski H, Hakala M. Good results from combining etanercept to prevailing DMARD therapy in refractory juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002;20: 867-70

V Haapasaari J, Kautiainen H, Isomäki H, Hakala M. Etanercept does not essentially increase the total costs of treatment of refractory JIA. *J Rheumatol* 2004;31: 2286-9

Abbreviations

ACR	American College of Rheumatology
ANA	antinuclear antibody
ARA	American Rheumatism Association
Anti-TNF	anti-tumor necrosis factor
AZA	azathioprine
CEA	cost-effectiveness analysis
CRP	C-reactive protein
CyA	cyclosporine
DMARD	disease-modifying antirheumatic drug
GSTM	gold sodium aurothiomalate
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
Hb	hemoglobin
HCQ	hydroxychloroquine
HLA	human leukocyte antigen
HRQoL	health-related quality of life
i.a.	intra-articular
ILAR	International League of Associations for Rheumatology
IL-1	interleukin 1
i.v.	intravenous
JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
QALY	quality-adjusted life-year
RF	rheumatoid factor
RFH	Rheumatism Foundation Hospital
s.c.	subcutaneous
SMR	standardized mortality ratio

SSZ

sulphasalazine

Abstract

Combination of cyclosporin (CyA) with the prevailing therapy was studied in 32 children with severe and refractory juvenile idiopathic arthritis (JIA). Although blood erythrocyte sedimentation rate (ESR) and the serum concentration of the C-reactive protein (CRP) improved significantly ($p < 0.05$ and < 0.001 , respectively), the hospitalization days, oral dose of prednisolon and intra-articular injections did not decrease. CyA may have a place in the treatment of uveitis in patients with JIA.

The effect of hydroxychloroquine (HCQ) on the serum concentration of methotrexate (MTX) in children with JIA was studied in 34 children receiving concomitant HCQ and MTX, and in 40 children with only MTX. No differences were seen in the serum concentration of MTX between the two groups. It was concluded that contrary to an earlier report, concomitant HCQ does not reduce the bioavailability of MTX.

The hepatotoxicity of long-term MTX treatment was studied in 34 children with JIA by blood transaminase concentrations and by histology of liver biopsy specimens. All patients with a weekly MTX dose lower than 20 mg/body surface square meter, evinced no signs of liver pathology. Out of ten patients on a higher MTX dose, four had mild pathological changes and one had markedly elevated blood transaminases. No irreversible changes were seen.

The efficacy and costs of a new antirheumatic drug, etanercept, were studied in 31 patients with severe and refractory JIA. Etanercept was combined with the prevailing drug therapy, which in 27 children also included MTX. The dose of etanercept was 0.4 mg/kg twice a week for 12 months. Significant improvements were seen in all parameters studied: daily dose of prednisolon ($P < 0.001$), number and dose of disease-modifying antirheumatic drugs (DMARDs) ($p < 0.001$) and number of intra-articular injections of glucocorticoids ($p < 0.001$), and level of ESR ($p < 0.01$) and CRP ($p < 0.05$). In two patients the treatment was discontinued because of adverse effects and in two because of lack of efficacy.

Etanercept increased the total annual costs of treatment by 2 716 US dollars per patient (10% of the total costs). This must be viewed against the background of reduced inflammatory activity in the joint disease and the probable reduction of lifetime pain and disability produced by the disease.

Introduction

Chronic arthritis in childhood (JIA) was formerly known as juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis (JCA). It is not one disease, but rather a group of inflammatory conditions of unknown etiology commencing in childhood. The main feature is synovial inflammation in one or several peripheral joints. Fever is common, anterior uveitis can be symptomless but detrimental, while other extra-articular manifestations such as carditis or pleuritis and rash are seldom presented. Disease severity varies from a mild monoarthritis to severe systemic disease with life-threatening complications.

Although the first reports of juvenile arthritis are from the mid-1800s (Bywaters 1977, Bywaters 1994), its etiology has not been resolved. Genetic susceptibility has a role in the etiology, and it seems to be associated with the major histocompatibility complex (Säilä et al. 2004), but also with other genes (Rundstadler et al. 2005). The type of onset of JIA in monozygotic twins can be phenotypically different (Säilä et al. 2000), which might indicate similar genetic risk factors in different disease types. However, it is possible that the genetic background and other etiological factors are not the same in different disease forms.

The diagnosis of JIA is made on clinical grounds by identification of inflamed joints and exclusion of other possible etiologies such as infections. In recent years, modern imaging techniques such as ultrasound and magnetic resonance imaging have facilitated the documentation of synovitis.

There is no curative treatment for JIA. The available modalities, however, are effective in respect of symptoms, disease progress and outcome. Treatment involves disease-modifying antirheumatic drugs (DMARDs), both systemic and intra-articular glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), orthopedic surgery, physiotherapy, guidance of bone growth by splints and orthoses, and psychosocial

support to the patient and family. The best possible education is important. On clinical grounds there is the impression that more intensive diagnostic approaches such as early admission and use of imaging methods, and an active policy in treating inflammatory joint diseases, i.e., use of intra-articular glucocorticoids and widespread use of methotrexate (MTX) and combinations of DMARDs, have reduced the need for orthopedic operations at the Rheumatism Foundation Hospital (RFH). Scientific evidence of this, however, is lacking.

The introduction of anti-tumor necrosis factor (anti-TNF) therapies at the beginning of this millennium has opened up completely new strategies in treatment. It is likely that new treatment principles will be developed in the near future. Control of the inflammation may be so efficient that no curative treatment is necessary. However, there remain and will occur severe and resistant cases, in whom surgery, orthoses, physiotherapy and rehabilitation are needed to prevent permanent deformity of the joint and decline in quality of life.

There has been increasing evidence of a better outcome in patients suffering from JIA since before anti-TNF therapies. Improvements have gone hand in hand with developments in treatment. Mortality due to JIA is decreasing and is not much different from that in the general population (Savolainen et al. 1993). Working ability can be retained fairly well, partly thanks to early occupational guidance and rehabilitation (Ylijoki 1998, Arkela-Kautiainen et al. 2005).

Autologous stem cell transplantation is still experimental and is warranted for the treatment of severe JIA cases refractory to conventional therapy. The procedure induces a drug-free remission in severely ill patients, but carries a significant mortality risk (de Kleer et al. 2004). Remission is possible even in cases, where previous treatment with anti-TNF agents has failed.

The paediatric department at the RFH in Heinola, Finland, was established in 1952. Most chronic cases with JIA in the whole country were treated at the department. Three early academic dissertation studies (Vainio 1956, Sairanen 1958, Laaksonen 1966) well describe the clinical features of JIA during that time. The study by Vainio included 35, that by Sairanen 100, and by Laaksonen 544 JIA patients. The patient material on RFH has since been utilized in a number of corresponding studies (Anttila 1972, Savolainen 1998, Kotaniemi et al. 2001, Laiho et al. 2002, Arkela-Kautiainen et al. 2005, Säilä et al. 2004, Skyttä et al. 2005).

The purpose of the present series was to describe our own experiences of DMARDs in the treatment of JIA and to compare the effects and costs of anti-TNF therapy with the traditional one in refractory cases of the disease.

Review of the literature

1. Classification

The first descriptions of juvenile arthritis are from the mid-19th century (Bywaters 1977, Bywaters 1994, Baum and Baum 1978). Georg Frederic Still presented his famous study in London in 1896 and it was published the following year (Still 1897). He well described systemic arthritis and distinguished two other disease types. However, no further serious attempts to classify juvenile arthritis were made for more than half a century. In addition, rheumatic fever as well as many joint infections such as tuberculosis may also have confused the diagnosis in practice.

The first modern classification criteria for juvenile arthritis were introduced in a Danish doctoral dissertation in 1952 (Sury 1952), but these criteria never gained general acceptance. The Taplow criteria were published simultaneously with the American Rheumatism Association (ARA) criteria for adult rheumatoid arthritis (Ansell and Bywaters 1959). ARA adopted the term juvenile rheumatoid arthritis (JRA) in accord with the adult disease (Brewer et al. 1972, Brewer et al. 1977). The term juvenile chronic arthritis (JCA) was accepted five years later by the European League Against Rheumatism (EULAR) (Wood 1978). The disease was called JRA in America and in some European countries, and JCA in Great Britain and most other European countries, including Eastern Europe. Since 1997 The International League of Associations for Rheumatology (ILAR) criteria have replaced both the EULAR and the ARA criteria, and are now in general use, as well as the term juvenile idiopathic arthritis (JIA).

Table 1. Diagnostic criteria for chronic arthritis in children

	Diagnostic criteria		
	EULAR	ARA	ILAR
Nomenclature for disease group	Juvenile chronic arthritis (JCA)	Juvenile rheumatoid arthritis (JRA)	Juvenile idiopathic arthritis (JIA)
JAS, IBD, JPsA	Included (listed separately)	Excluded	
Duration of symptoms necessary for diagnosis	3 months	6 weeks	6 weeks
Age of patients at disease onset	0 – 15 years	0 – 15 years	0 – 15 years
Exclusion of other diseases	Yes	Yes	Yes
Division into onset subtypes at 6 months disease duration	Yes	Yes	Yes

Abbreviations: ILAR=International League of Associations of Rheumatologists; JAS = juvenile ankylosing spondylitis; IBD = arthropathy associated with inflammatory bowel disease; JPsA = juvenile psoriatic arthropathy

1.1. The ILAR classification 1995

In the 1995 criteria JIA was divided into seven relatively homogeneous, mutually exclusive categories based on predominant clinical and laboratory features (Fink 1997).

1.2. The first revision of the ILAR criteria (Durban 1997)

An eighth category was added: other arthritis for patients not fitting any other category or more than one category. This solved the common problem of placing patients not exactly fitting any of the categories or fulfilling the criteria of more than one category. Studies applying these criteria report that 11.6 – to 23 % of patients fall into “ other” category (Petty et al. 1998).

1.3. The second revision of the ILAR criteria (Edmonton 2001)

There have been several minor changes since the first revision. From a clinician's point of view removal of the requirement that a dermatologist make the diagnosis of psoriasis and that there must be medical confirmation of HLA-B27-associated disease in a relative constitute the most facilitating changes (Petty et al. 2004).

General definition of JIA

Juvenile idiopathic arthritis is an arthritis of unknown etiology with onset before the 16th birthday and persisting for at least 6 weeks; other known conditions are excluded.

Exclusions

The principle in this classification is that all categories of JIA are mutually exclusive. This is reflected in the list of possible exclusions for each category:

- a. Psoriasis or a history of psoriasis in the patient or first-degree relative.
- b. Arthritis in an HLA-B27-positive male beginning after the 6th birthday.
- c. 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.
- d. The presence of IgM rheumatoid factor (RF) on at least 2 occasions at least 3 months apart.
- e. The presence of systemic JIA in the patient.

The application of exclusions is indicated under each category, and may alter as new data become available.

Categories:**Systemic Arthritis**

Definition: Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration 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.

Exclusions: a, b, c, d.

Oligoarthritis

Definition: Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognized:

1. Persistent oligoarthritis: Affecting not more than 4 joints throughout the disease course.
2. Extended oligoarthritis: Affecting a total of more than 4 joints after the first 6 months of disease.

Exclusions: a, b, c, d, e.

Polyarthritis (Rheumatoid Factor-Negative)

Definition: Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative.

Exclusions: a, b, c, d, e.

Polyarthritis (Rheumatoid Factor-Positive)

Definition: 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.

Exclusions: a, b, c, e.

Psoriatic Arthritis

Definition: Arthritis and psoriasis, or arthritis and at least 2 of the following:

Dactylitis
Nail pitting or onycholysis
Psoriasis in a first-degree relative

Exclusions: b, c, d, e.

Enthesitis-related arthritis

Definition: Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:

The presence of or a history of sacroiliac joint tenderness and/or inflammatory low back pain

The presence of HLA-B27 antigen

Onset of arthritis in a male over 6 years of age

Acute (symptomatic) anterior uveitis

History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative

Exclusions: a, d, e.

Undifferentiated arthritis

Definition: Arthritis fulfilling criteria in no category or in 2 or more of the above categories.

Descriptors

A number of "descriptors" have been proposed to gather further information on the patterns of the clinical picture. These include age at onset, further features of the arthritis (large joints, small joints, symmetry, upper or lower limb predominance, and individual joint involvement), disease course (number of joints), presence of ANA, chronic or acute anterior uveitis, and the HLA allelic associations. The potential value of ANA as a diagnostic criterion has received a great deal of attention, but there is insufficient evidence to support its inclusion at this time. The descriptors are not part of the classification of JIA, but new data on them may allow reclassification in the future.

Definition of Terms

Arthritis: Swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, which persists for at least 6 weeks, is observed by a physician, and is not due to primarily mechanical disorders or to other identifiable causes.

Dactylitis: Swelling of one or more digits, usually in an asymmetric distribution, which extends beyond the joint margin

Enthesitis: Tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.

Inflammatory low back pain: Lumbosacral spinal pain at rest with morning stiffness that improves on movement.

Nail pitting: A minimum of 2 pits on one or more nails at any time.

Number of affected joints: Joints which can be individually evaluated clinically are counted as separate joints.

Positive test for rheumatoid factor: At least 2 positive results (as routinely defined in an accredited laboratory), at least 3 months apart, during the first 6 months of disease.

Psoriasis: As diagnosed by a physician (but not necessarily by a dermatologist).

Quotidian fever: Fever rising to $> 39^{\circ}\text{C}$ once a day and returning to 37°C between fever peaks.

Serositis: Pericarditis and/or pleuritis and/or peritonitis.

Sacroiliac joint arthritis: Presence of tenderness on direct decompression over the sacroiliac joints.

Spondyloarthropathy: Inflammation of entheses and joints of the lumbosacral spine.

Uveitis: Chronic anterior uveitis as diagnosed by an ophthalmologist.

2. Review of juvenile idiopathic arthritis (JIA) in the literature and the author`s own experience

2.1. Epidemiology of JIA

The incidence of JIA appears to vary between 10 and 20 cases per 100 000 children per year (Anderson Gäre and Fasth 1992, Moe and Rygg 1998). In Finland figures from 14 (Kaipiainen-Seppänen and Savolainen 1996) to 18.2/100 000/year (Kunnamo 1986) have been obtained. The incidence of systemic arthritis seems to be similar in most populations, but other disease types may have more varying genetic or other risk factors, and there are differences in incidence in different populations.

Oligoarthritis constitutes 60% of all cases and polyarthritis 30% (Cassidy & Petty 2005).

Evaluation of incidence is sensitive to methodology. Investigation in a given population yields higher incidence figures than counting cases in hospitals. The mean annual incidence of juvenile rheumatoid arthritis among children referred to pediatric rheumatology centers in Austria was only 4.3/100 000 (Huemer et al. 2001). Population-based incidence figures for juvenile chronic arthritis are shown in Table 2.

In a recent study from the Nordic countries the incidence was lowest in Iceland (7/100 000), 9 and 16 from two different areas in Denmark, 15 in Sweden, 21 in Finland, and 19 and 23 from two different areas in Norway (Berntson et al. 2003).

A review of 34 epidemiological studies of the worldwide prevalence of JIA found figures from 7 to 401/100 000 (Manners and Bower 2002). The major factors contributing to the marked differences are probably technical. As noted, community-based studies give higher results than clinical case studies.

In community-based studies the prevalence varies from 65 to 86 per 100,000 children (Sullivan et al. 1975; Andersson Gäre 1992). The first study to assess the prevalence of the disorder in Finland was carried out by Laaksonen, using a hospital series and estimating a prevalence of 80/100 000 (Laaksonen 1966). Lantto and von Wendt (1985) found a similar prevalence (78/100 000) in a population-based series in Northern Finland. The first report on a Chinese population in Taiwan gave a prevalence of 3.8/100 000 (Huang et al. 2004), however. Prevalence was the same in boys and girls.

Table 2. Population-based incidence of juvenile chronic arthritis

Reference (first author)	Country	Study period	Diagnostic criteria	Number of incident cases	Incidence (/100 000)
Towner 1983	Rochester Minnesota	1960 – 79	ARA EULAR	41 31	13.9 10.5
Lantto 1985	Finland	1980 – 84	ARA	107	12.7
Kunnamo 1986	Finland	1982 – 83	ARA ARA*	29 27	19.6 18.2
Andersson Gäre 1992	Sweden	1984 – 88	EULAR	213	10.9
Peterson 1996	Rochester Minnesota	1980 – 93	ARA	65	7.8
Moe 1998	Norway	1985 – 94	ARA	109	22.6
Kaipainen-Seppänen 1996	Finland	1980 1985 1990	ARA ARA ARA	38 40 36	13.8 15.1 13.5
Huemer	Austria	2001	EULAR	107	4.28

*Arthritis of three months' duration required

2.2. Clinical findings in JIA

2.2.1. Clinical picture

The main clinical feature of JIA is arthritis in one or more joints. This is often associated with pains and functional difficulties. While all synovial joints in the body can be inflamed, the main difficulties arise from destruction of the large joints. There are special features of chronic arthritis in children, in whom skeletal growth still continues.

Flexion contractures of hip and knee joints earlier reached extreme dimensions, but many children were able to walk although buttock was descended close to the heel. Today these contractures are no longer encountered.

Bone growth takes place in the epiphyseal plate in the periarticular area, and joint inflammation may result in changes in its function. In the small joints, for example those in fingers and toes, the function of the epiphyseal plate will retard or discontinue with permanent suppression of growth, while in large joints such as knee, its function may be activated, resulting in asymmetrical growth of the lower limbs. The acceleration of growth is probably caused by the elevated temperature in the inflamed joint. Thus, growth is faster on the medial side, and the result is not only a longer lower extremity but also a valgus deformity.

Apophyseal joint ankylosis at multiple levels is the most frequent inflammatory change in the cervical spine in patients with JIA (Laiho et al. 2002). In patients with refractory arthritis complicated by secondary amyloidosis 86% of patients evince some radiological changes, 63% apophyseal joint ankylosis and 57% atlantoaxial impaction (Laiho et al. 2001).

Synovial inflammation in ankle and foot joints may result in rapid joint destruction, restriction of movements and severe permanent deformities (Vainio 1956). The talus can turn to vertical position, resulting in total loss of the foot vault and planovalgus deformity. Sometimes, with elevation of the first metatarsal bone a banana-like varus deformity of the foot takes place.

Tempomandibular joint inflammation is usual. Permanent inflammation is associated with mandibular growth disturbances and restriction in mouth opening and disturbed bite. Micrognathia was formerly a typical and visible sign of JIA.

The occurrence of anterior uveitis in JIA patients was 16 per cent in a Finnish retrospective study (Kotaniemi et al. 1999). During a follow-up time of 4.5 years, 24% of patients with a newly diagnosed JIA developed uveitis at our clinic (Kotaniemi et al. 2001, I). In 99 out of 104 cases uveitis was asymptomatic. JIA was seen in 14 out of 174 uveitis patients (8%) included in the Finnish Register of Visual Impairment (Kotaniemi et al. 2001, II).

Serositis is a common manifestation of systemic disease. Pericarditis may be severe and life-threatening but usually responds to glucocorticoids.

Fever is one of the cardinal signs of systemic-onset JIA, but it can also be seen also in other types with a high inflammatory activity. Before modern treatments fever often continued for months in Still's disease, but today large-dose glucocorticoids and use of anakinra, an inhibitor of interleukin-1 (IL-1), a cytokine produced by synovial macrophages, suppress it rapidly (Pascual et al. 2005).

2.2.2. Complications of JIA

Amyloidosis has been an important cause of death in JIA (Laaksonen 1965, Ansell and Wood 1976, Ylijoki 1998). It is a complication of a persistent active disease. Amyloid fibrils accumulate in tissues and cause organ failure such as renal insufficiency. Mortality due to amyloidosis has decreased parallel with more active use of DMARDs (Schneider & Passo 2002).

Decreased statural growth in JIA was already mentioned by Still (1897). In a large patient sample studied by Stoeber (1981) shortness of stature was observed in 10%, in a Swedish sample of systemic-type juvenile arthritis in as many as 39% (Svanteson et al. 1983).

2.3 Outcome of JIA

As the clinical picture of JIA so its outcome is heterogeneous. Outcome measures have recently been reviewed (Duffy 2005).

In general, female gender, polyarticular and symmetrical joint involvement, elevated inflammatory markers and rheumatoid factor positivity have been the most consistent predictors of a poor outcome (Adib et al. 2005, II). However, there are no certain means for early assessment of prognosis in individual cases.

Even in the 1930s JIA was still an extremely disabling disease. A Finnish study identified 254 cases with chronic arthritis with a disease onset at ages of 16 years or younger. Seventy per cent of these were “totally or almost totally incapacitated”, although the most severe cases had died of the disease and the study did not cover all cases in the country (Paloheimo 1941). Disabilities derived mainly from ankylosing deformities of joints, because with the development of ankylosis inflammation abated, the patient avoided systemic complications and survived.

Although the mortality rate among children with JIA is estimated to be low, e.g. less than 0.3% in North America, this is nonetheless significantly higher than the standardized death rate for age (Wallace & Levinson 1991). Approximately two-third of deaths occur in children with systemic-onset JIA, which accounts for only 10 to 20% of all JIA (Wallace & Levinson 1991). The excess mortality was previously mainly due to secondary amyloidosis, infections and carditis (Ansell and Wood 1976, Stoeber 1981). Amyloidosis was responsible for substantially higher mortality in earlier European studies (Laaksonen 1966, Ansell & Wood 1976, Stoeber 1981), but there has been a sharp decline in the frequency of this complication and associated deaths (Savolainen & Isomäki 1993). All this took place before the introduction of anti-TNF therapies.

In the 1930s the ten-year mortality was about 25%, and remained at 5-10 per cent in the 1960s to 1980s (Ylijoki 1998). Subsequently no deaths were observed among 124 JIA patients during seven year's follow-up in Sweden (Anderson Gäre and Fasth 1995). In Scotland between 1981-2000, the standardized mortality rate (SMR), i.e., the ratio of observed to expected deaths, in patients with JIA was 3.4 for men and 5.1 for women. These were the highest figures among all six rheumatic conditions studied, including RA (Thomas et al. 2003).

In Finland the mortality rate and causes of death among all Finnish patients with juvenile arthritis were studied in 1969-1979 and 1980-1990 (Savolainen et al. 1993). SMR during the periods in question was 2.7. and 2.4, respectively. The decline in mortality was due mainly to the diminution of secondary amyloidosis as a cause of death. There has been no recent study assessing trends in mortality in JIA in Finland.

Physical disability has usually been measured by the Steinbrocker scale (Steinbrocker et al. 1949). There seems to have been a slight improvement in functional capacity from the 1950s to the 1990s (Ylijoki 1998). Adib and associates (2005, I) analyzed 21 outcome studies from the last 10 years. Outcome was measured mainly by remissions, loss of function and structural damage. The authors concluded that there remains a considerable lack of clarity in prognosis following the onset of JIA for the major outcomes, although patients with oligoarthritis at presentation have the best prospects.

Follow-up studies have shown that in early adulthood more than half of all patients are today symptomless (Ylijoki 1998, Arkela-Kautiainen et al. 2005). Current social functioning and health-related quality of life (HRQoL) were similar in young adult Finnish JIA patients diagnosed during 1976-1995 at the RFH compared to age-, sex- and municipality-matched controls (Arkela-Kautiainen et al. 2005). However, patients with extended oligoarthritis attained significantly lower scores in the physical and mental items of HRQoL than oligo- or polyarthritic patients. It is also to

be noted that the level of work disability was similar among patients and controls (Arkela-Kautiainen, personal communication). Thus, the outcome has markedly improved during recent decades.

2.4. Drug treatment of JIA

2.4.1 Development of drug treatment in JIA

The history of drug treatment for JIA can be divided according to certain major drug innovations which have had an impact on the outcome of the disease. These few drugs describe step by step the general development of drug treatment in JIA.

The aspirin (acetylsalicylic acid) era commenced as far back as 1880s, when pyrazoles (antipyrin, pyramidol) and para-aminophenols (acetanilide, phenacetin, paracetamol) were introduced in Germany. The anti-inflammatory effects of these drugs are weak, however, and most of them are quite toxic. Phenacetin was in very common use until the 1960s and paracetamol is still one of the most important antipyretic drugs for children everywhere.

In 1897 Felix Hoffmann synthesized acetylsalicylic acid or aspirin, which was the main drug for millions of rheumatic patients for half a century. Credit for the discovery of aspirin has been challenged since World War II (Sneider 2000). (The letters in the drug's name come from acetyl (A), from the plant *Spirea ulmaria*, the source of salicylate (SPIR), with IN as the end of the word.)

Aspirin is an effective analgetic if taken in doses large enough, but it probably has no effect on the outcome of JIA. Especially in small children it can cause serious adverse effects not properly documented at the introduction of Aspirin. The main benefit of Aspirin may have been amelioration of fever, pain and suffering. Today other NSAIDs have replaced Aspirin in children.

The glucocorticoid era started in 1949, when hydrocortisone was discovered for the treatment of adult rheumatoid arthritis (RA), and it still retains a role. It must have been amazing to see the first results of glucocorticoids in the early 1950s, when Aspirin was the only effective drug in most rheumatological clinics.

Synthetic glucocorticoids have certainly had an impact on the outcome of JIA. However, intramuscular gold gradually gained place in adults, as well as antimalarial drugs. These were also actively used in children. Correction of disabilities by orthopedic surgery commenced on a large at the RFH in the 1950s (Vainio 1956). Thus, all credit for the beneficial development in the treatment and outcome of JIA cannot be given to glucocorticoids.

Probably the first important effect of glucocorticoids in JIA was the decline in carditis mortality in the 1950s and 1960s (Stoeber et al. 1967). Another positive effect was achieved by intra-articular (i.a.) administration of slowly dissolving prepartes. This form of therapy has developed over the decades to become a highly effective tool in the prevention of disabilities and joint deformities. Today, every one swollen joint or tendon sheath is an indication for an injection in a patient with JIA.

It is not clear to what extent peroral glucocorticoids have improved the outcome of JIA. Before the MTX era amyloidosis was common despite the wide use of glucocorticoids. Adverse effects of glucocorticoids were common, but disabilities were probably on the decline before the widespread adoption of MTX.

The era of immunosuppressive drugs and DMARD combinations opened gradually during the 1960s, when the first reports on azathioprine (AZA) (Massimo et al. 1966, Stoeber et al. 1967) and chlorambucil (Ansell et al. 1971) in severe JIA were published. Development was slow in the 1970s, and only in the mid 1980s were the first studies of MTX published (Truckenbrodt and Hafner 1986). Kvien and colleagues (1986) had also

found improvements in most of the activity measurements in JIA patients treated with AZA, but the authors concluded that AZA remains a third-line drug in JIA patients.

The attitude to MTX gradually became more optimistic. Positive results were reported, and in 1989 Wallace and associates (1989) published comforting data on the toxicity of MTX in children. A large USA-USSR cooperative study of MTX was published (Giannini et al. 1992), and at the latest thereafter MTX became the main drug used in JIA.

At our hospital, the very first child treated by AZA in 1978 was a two-year-old girl with highly active Still's disease. This particular patient was selected for the first experiment, as her father was a physician who understood the potential advantages of this new and still frightening therapy. Fortunately, AZA splendidly demonstrated its therapeutic power; the child has since been quite well.

The first report of the effect of a combination of DMARDs in the treatment of inflammatory joint disease came from adult RA in the RFH as early as 1963 (Sievers et al.). In practice, however, the idea of combinations of several DMARDs and glucocorticoids was introduced in the 90s (Furst DE 1990, Möttönen et al. 1999). Combinations as well as early and aggressive treatment policies were soon adopted for JIA. MTX and hydroxychloroquine (HCQ) form the basis of combinations, but in individual cases several other DMARDs have been successfully applied.

There is a clinical impression that the results of treatment of JIA have been downright astonishing during the last few decades. Disabilities and growth retardations, severe flexion contractures and dysformed feet as well as secondary amyloidosis have almost disappeared at our clinics. In fact this phenomenon was already reported in a series of cases diagnosed in the 60s and 70s, when compared with historical controls (Ylijoki 1998). There is, however, conflict in the results of outcome studies, possibly attributable to differences in disease classification, patient selection

methods, follow-up duration, assessment methods used and not least, the lack a generally accepted definition of remission in JIA (Schneider & Passo 2002).

Not all credit for this positive development in the outcome of JIA can be given to cytotoxic drugs in general and MTX in particular. The mode of thinking has also changed, and this may have influenced the outcome more. It has been observed that tenacious treatments with i.a. injections, surgery, guiding of bone growth by splints and orthoses, physiotherapy and rehabilitation are of benefit, and it has also been realised that effective treatment is profitable. The realistic goal of treatment is now more often remission.

The era of biological agents opened simultaneously with the present millennium. This approach is based on biotechnological innovations which have been applied in clinical medicine with remarkable success; results from this short period of time are highly promising, and although the new remedies influence some very basic physiological functions of the body, no alarming adverse effects have appeared.

New biological agents affecting an expanding range of physiological functions will obviously be developed, and pharmacogenetics may come to play a role. It is possible that for an individual patient with a certain disease type a combination of drugs from a large palette will be selected. The particular combination may include inhibition of TNF, some other cytokines, angiogenesis, neutrophil mobilization, macrophage functions etc., or again stimulation of some other functions. Even the first experiences with TNF and IL-1 inhibition have markedly changed the therapeutic possibilities in JIA. The different actions of these agents in systemic onset JIA is an example prompting a search for specific drugs for different types of arthritis in future pediatric rheumatology.

2.4.2 Glucocorticoids

Cortisol was discovered in 1949 as a means of treating RA in adults (Lundberg et al. 2004). It was also found effective in juvenile patients. Cortisol was soon replaced by synthetic steroids, which have a weaker mineralocorticoid effect and a longer half-life in the body. Today glucocorticoids remain the most potent anti-inflammatory drugs in JIA, although their effect is of short duration.

The main therapeutic effect of glucocorticoids is suppression of inflammation. As a result, fever, pains and joint swellings disappear and subjective well-being improves. One of the first benefits of glucocorticoids in JIA was a decline in carditis mortality in the 1950s and 1960s (Stoeber 1976).

At the onset side-effects were common and serious, even horrific: retardation of stature growth, Cushing habitus, osteoporosis with multiple vertebral collapses and further decline in height, cataracts, diabetes and hypertension. Adrenal cortex atrophy was sometimes fatal, appearing in stressful situations, e.g. when orthopedic operations were carried out. In order to prevent cortical atrophy, ACTH was introduced; its mineralocorticoid effects were, however, intolerable and it remains unclear whether glucocorticoid treatment did more harm than good in the early years of the cortisone era.

With advancing experience the appropriate mode of glucocorticoid treatment was learned. The alternate morning schedule allows normal growth and is sufficient for therapeutic aims. The glucocorticoid dose can be diminished by using DMARDs. Deflazacort seems to have fewer adverse effects on bone than prednisolone (Loftus et al. 1993).

2.4.3 Intra-articular glucocorticoids

The importance of i.a. glucocorticoids in the treatment of chronic arthritis has been recognized during the last decades. Their increased use in treatment may be due partly to the advent of long-acting preparates, especially triamcinolone hexacetonide. Its dose is 5 to 40 mg depending on the size of the joint. In some studies even 82 per cent of treated joints have shown remission of joint inflammation lasting more than 6 months after a single injection (Padeh and Passwell 1998). In a series of 79 children with JIA and early phases of knee joint synovitis, the probability of a patient staying in remission was much higher in triamcinolone-treated patients than in those receiving methylprednisolone (Honkanen et al. 1993). After 12 months 32% of tarsal area synovitis and 50% of hip synovitis were in remission after intra-articular glucocorticoid (Tynjälä et al. 2004).

In the case of young children it is a general clinical practice for i.a. injections to be given under general anesthesia. Ultrasound-guided injections are needed especially for hip joints, but the procedure also ensures successful injection in other joint areas. The effect of i.a. glucocorticoids is usually short if the general inflammatory activity is high. The therapeutic effect is best in cases with synovitis of short duration, as shown in studies on early oligoarthritis in adults (Green et al. 2001).

The principle in the Department of Pediatrics at the RFH is that all clinically significant joint or tendon sheath inflammations are immediately treated by local injections. Ultrasound has greatly improved the identification of early synovitis.

The side-effects of i.a. glucocorticoids are usually mild. Children learned to tolerate the injections even before anesthesia was used. However, repeated injections with high doses have systemic effects and this must be taken into account in the planning of a comprehensive treatment policy.

2.4.4 Gold compounds

Intramuscular gold, mainly in the form of gold sodium thiomalate (GSTM), was widely used in rheumatoid arthritis in adults from the 1930s. It is an effective drug, but adverse effects, though usually mild, are common. Gold was adopted from adults for clinical use in the treatment of JIA. Its use was not limited to seropositive polyarthritis in children with JIA. There are as yet no placebo-controlled studies of GSTM in JIA patients. In a retrospective study of 51 JIA patients a reduction in the total number of involved joints was seen in 49% of patients. Patients who responded experienced considerable improvement (Brewer et al. 1980).

Clinical experience advocates intramuscular GSTM administered at 1 mg/kg weekly until remission in the treatment of JIA. Gold therapy must be discontinued in up to 36 % of JIA patients on account of adverse effects (Sairanen & Laaksonen 1962, Ylijoki 1998). Its combination with HCQ is well known (Sievers et al. 1963). The use of gold has become less frequent since the introduction of MTX.

The peroral gold compound auranofin has been studied in one double-blind and placebo-controlled trial (Giannini et al. 1990). No significant differences were observed between the placebo and auranofin groups during six months.

2.4.5 Chloroquine, hydroxychloroquine (HCQ)

The use of chloroquine is not widespread mainly by reason of frequent side-effects. Permanent damage to the retina is rare, but transient precipitation of chloroquine on the surface of the cornea is common (Neubauer et al. 2003)

HCQ is better tolerated. The initial daily dose of HCQ is 5mg/kg up to 300-400 mg. A large multicenter study evaluated the efficacy of HCQ and penicillamine in the treatment of JIA during a 12-month trial (Brewer 1986).

Pain on movement was the only index of articular disease alleviated more by HCQ than by placebo. No other significant differences were found between HCQ, penicillamine or placebo.

Mild side-effects are common. HCQ is frequently used in combination with MTX, as some data show that HCQ may prevent transaminase elevations during MTX therapy (Fries et al. 1990).

2.4.6 Methotrexate (MTX)

MTX was one of the first synthetic cytotoxic drugs. In addition to use in malignancies, it was also tried in psoriatic arthritis as early as the 1950s and subsequently in RA (Rothermich 1967), but its reintroduction as an antirheumatic drug did not take place until the 1980s. The first controlled trials were on adult patients (Weinblatt DE et al. 1985), but it was soon also adopted in pediatric clinics.

Giannini and associates (1992) published a Soviet-American co-operative study of the efficacy of MTX in refractory juvenile arthritis. The study was double-blind and included a placebo group, being than the very first placebo-controlled drug trial in JIA. According to a composite index of a number of response variables, 63 % of the children who received low-dose MTX (10 mg of the drug per square meter of body-surface area) showed improvement as compared to 32 % of those in the very-low-dose (5 mg per square meter) group and 36 % of those in the placebo group ($p < 0.05$). After this study pediatric rheumatology proceeded to a new era where MTX is the gold standard, often used in combination with HCQ.

Absorption of MTX from the ileum is not consistent, and in different patients the absorption rate can vary substantially. The drug should be administered subcutaneously when used in a higher dosage (0.65 to 1.0mg/kg) the maximum dose being 30 mg/week (Wallace & Sherry1992).

The most common side-effects are liver enzyme elevations and nausea, sometimes so severe and reflexive that the very colour of the tablet induces vomiting. Severe adverse effects are rare in the doses used today, but careful monitoring is necessary. MTX is a folic acid antagonist, and side-effects can be reduced by oral folic acid substitution without loss of effect. There is no consensus as to the dosage and timing of folic acid administration.

2.4.7 Azathioprine (AZA)

In a placebo-controlled study a group under Kvien (1986) reported that AZA treatment induced significant improvements in disease activity measures during a 16 weeks' trial. According to experience in our clinic AZA is a useful drug in JIA, with acceptable side-effects (Savolainen et al. 1997). Even in cases with incomplete remission it has a glucocorticoid-sparing effect. The use of AZA is declining due to the well-documented efficacy of MTX and its widespread use. The usual daily dose is 3 mg/kg. The adverse effects are expected and not severe.

2.4.8 Cyclosporine (CyA)

There are scant data on the use of cyclosporine (CyA) in JIA. Ostensen and colleagues (1988) reported in an open trial that its effect was mainly symptomatic and temporary. Side-effects such as a marked rise in serum creatinine were common. In one other report on CyA in the treatment of systemic onset JIA withdrawal due to inefficacy or side-effects took place in over 60% of cases, but on the other hand, 24 per cent of patients achieved complete remission (Gerloni et al. 2001). A retrospective study of 22 patients with refractory JIA showed that 3.2 mg/kg/day of CyA for 16 months was well tolerated. The use of prednisolone could be discontinued in five out of 20 patients and its dose could be reduced by more than 50% in ten patients (Reiff et al. 1997).

2.4.9 Sulphasalazine (SSZ)

Only one placebo-controlled double-blind study of the efficacy of sulphasalazine (SSZ) in JIA has been published (van Rossum et al. 1998). In this multicenter trial SSZ at a dosage of 50 mg/kg/day was superior to placebo. Adverse effects were more frequent in the SSZ group and were the main reason for withdrawals. No serious side-effects were seen, however.

Several uncontrolled studies report some SSZ-associated benefits in all subtypes of JIA (Brooks 2001). Promising results have been recorded in chronic uveitis in children with JIA (Huang et al. 1997).

SSZ has been reported to depress fertility in men and experimental animals (Steeno 1984), which constitutes a reason to avoid its use in young male patients with JIA. In rats SSZ seems to depress sperm motility and acrosome reaction, thereby leading to infertility (Fukushima et al. 2005).

2.4.10 Leflunomide

Only two controlled studies of leflunomide in JIA have been published. Gao and associates (2003) compared MTX and leflunomide together with MTX alone in 40 patients with active polyarticular JIA. The remission rate at week 26 was 38% in the drug combination group and 0% in MTX alone. No difference was observed in the occurrence of side-effects. The authors concluded that a combination of leflunomide and MTX is better than MTX alone in JIA.

Silverman and colleagues (2005) compared leflunomide and MTX in a multinational, randomized, controlled trial involving 94 patients with polyarticular JIA. Both drugs resulted in high rates of clinical improvement, but the rate was slightly greater for MTX.

2.4.11 Chlorambucil

Chlorambucil is an alkylating agent which has been used in the treatment of adult RA since the 1960's (Renier et al. 1967). Ansell and associates (1971) reported the first experiences in JIA. They documented prolonged survival in JIA patients with amyloidosis, and its main indication has since been secondary amyloidosis. Miserocchi and group (2002) reported on 28 patients with chronic uveitis treated by chlorambucil. A positive clinical response was observed in 19 of them (68%). At our clinic, Savolainen has reported satisfactory clinical results, but serious side-effects were common (Savolainen 1998).

Overall, literature lacks documented data on the anti-arthritic effect of the drug, while clinical experience has been satisfactory. Severe-side effects such as infections and secondary malignancies have restricted its value. Some reports mention secondary leukemia in JIA after treatment with chlorambucil (Buriot et al. 1979; Kauppi et al. 1996).

2.4.12 Combination therapy with DMARDs

There are abundant of publications on the treatment of adult RA with combinations of different DMARDs. The studies in question show that the combination is more effective than a single drug. The FIN-RaCo study comparing SSZ, HCQ, MTX and low-dose prednisolone with the single drug strategy has been one of the key works in the area, and has induced clinical practice to adopt early treatment of RA in Finland (Möttönen et al. 1999). The increase in side-effects has not been prominent, probably by reason of the lower dosage of single drugs in combination (Möttönen et al. 1999).

There are very few reports on combination treatment with DMARDs in JIA patients, although combinations have been commonly used in clinical practice. Results of a combination of MTX and CyA for 6 to 30 months in

17 patients showed that two patients achieved complete disease control and five a 70% improvement as assessed by pediatric ACR criteria. Side-effects were common, but no treatment cessations were necessary (Ravelli et al. 2002).

The most frequent combination in children in our hospital is MTX-HCQ. Other combinations have been used mainly in refractory cases in the later course of the disease. The particular effects of different combinations are not clear. On a clinical basis it seems that JIA patients tolerate the various combinations well.

2.4.13 Biological agents

Two main strategies are employed to neutralize TNF- α in the current treatment strategy with biological agents involving either monoclonal IgG class antibodies to TNF or a soluble TNF- α receptor. Infliximab is a chimeric and adalimumab a fully human monoclonal antibody. Etanercept is a fully human, dimeric protein containing the extracellular domain of the human p75 TNF-receptor fused to the Fc region of human IgG1. By binding to TNF- α in the circulation, etanercept prevents the interaction of TNF- α with its cell surface receptor, thereby preventing cell activation and perpetuation of the inflammatory cascade. Etanercept differs from the other TNF- α modulators in that it also binds lymfotixin- α , thus blocking its interaction with cell-surface receptors. The structural differences go far to explain the many differences among these drugs in vitro and in vivo (Mpofu et al. 2005).

There are scant published data on the clinical use of etanercept in JIA. A two-part, multicenter trial of etanercept in children with active polyarticular JIA refractory or intolerant to MTX therapy reported etanercept to be effective and well tolerated (Lovell et al. 2000). In the first part of the study, where all patients received open-label etanercept at 0.4 mg/kg subcutaneously twice weekly for 90 days, 74% achieved the JIA 30 %

definition of improvement by pediatric ACR criteria. In the double-blind section of the study, where the responders were randomized to either placebo or etanercept, a significant difference was seen in the disease flare frequency between the groups, with percentages of 81 % and 28 %, respectively. There were no significant differences between the two treatment groups in the frequency of adverse reactions, injection site reactions being most common in the active group. Almost all patients continued the treatment for two years, when 69, 67, and 57% demonstrated 30, 50, and 70% improvement by pediatric ACR criteria, respectively (Lovell et al. 2003).

Infliximab and adalimumab have not been studied in double-blind, placebo-controlled trials in patients with JIA. In an open-label study 24 young adults with long-lasting, refractory JIA received weekly subcutaneous MTX and intravenous infliximab for two years. Significant improvements were observed in the inflamed joint count, pain score, patient's global and physician's global assessments, erythrocyte sedimentation rate and serum C-reactive protein concentration (Gerloni et al. 2005). Twelve patients experienced adverse effects and five withdrew (20.8%).

A randomized , placebo-controlled double-blinded clinical trial of etanercept in patients with systemic JIA is ongoing. Its effect has not been studied in recent-onset disease.

In a non-randomized, prospective, open-label study, 24 children with polyarticular JIA were treated with either infliximab (n=14) or etanercept (n=10) (Lahdenne et al. 2003). At 12 months, the pediatric ACR 75% improvement was achieved in 67% by both drugs. Five patients in the infliximab group had to withdraw because of side-effects and one due to lack of compliance in the etanercept group.

Interleukin 1 (IL-1) has a special pathogenetic role in systemic-onset JIA (Pascual et al. 2005), in which TNF blockers are not particularly effective.

The recombinant IL-1 receptor antagonist anakinra was given to nine children with systemic-onset JIA refractory to other therapies. Complete remission was obtained in seven and partial remission in the remaining two (Pascual et al. 2005). Anakinra also appears to be highly effective in adult Still's disease (Fitzgerald et al. 2005).

In the USA, the annualized risk of tuberculosis during the first 90 days of anti-TNF therapy was 95 cases per 100 000 person years for infliximab and 11 cases per 100 000 for etanercept (Wallis et al. 2004, I and II). The incidence of tuberculosis in the whole US population was 5 per 100 000 person years (Wallis et al. 2005). Thus the risk of granulomatous infections, including tuberculosis, increases with TNF inhibition, but because of the different mechanism of action, the risk is higher with infliximab and adalimumab than with etanercept (Wallis et al. 2005, Mpofo et al. 2005).

An increase in the incidence of lymphomas has been observed in adult patients with rheumatoid arthritis treated by TNF- α modulators (Wolfe and Michaud 2004, Geborek et al. 2005). The increase may however be biased in that patients with more severe arthritis with a higher risk of lymphoma preferentially receive anti-TNF therapy. Current data are insufficient to establish a causal relationship between the use of TNF blockers and the development of lymphoma. The overall long-term safety of these drugs is thus unknown.

2.5. Cost-effectiveness of biological agents

The aim of cost-effectiveness analysis (CEA) is to facilitate the allocation of limited health resources and to inform decision-makers. The exceptionally high costs of the new biological agents have made them obvious candidates for such analyses. Bansback and associates (2005) carried out a Medline search and identified six original CEAs evaluating TNF- α antagonists in RA in adults. Common to all studies was the lack of data from long-term randomized studies in which efficacy and resource consumption in comparison with standard care has been investigated.

Fautrel and colleagues (2005) found the direct costs of etanercept and infliximab to be similar in French patients, but the mean costs of administration varied considerably between the three hospital centers investigated. The authors concluded that the financial burden of biological treatments for adult rheumatoid arthritis is strongly influenced by substantial heterogeneity in medical practices.

Several cost-of-illness studies have been carried out over the past 20 years to estimate the annual costs of RA in adults (Cooper 2000), while in JIA such studies have been few.

A comprehensive review of the effectiveness and costs of etanercept in JIA has been carried out by Cummins and associates (2002). The benefit for a patient starting on etanercept rather than placebo was estimated to be 1.74 quality-adjusted life-years (QALYs), with a total discounted cost per QALY of 16 082 English pounds. The authors conclude, however, that the validity and accuracy of the analysis must be questioned in view of the lack of information on the long-term outcome and quality of life in JIA in particular.

3. Purposes of the present study

The main aims of the present study were

1. to investigate the effect of CyA combined to prevailing drug treatment in JIA patients
2. to investigate the possible effect of HCQ on the absorption of MTX in JIA patients
3. to assess the hepatotoxicity of MTX by percutaneous liver biopsy in patients receiving the drug at weekly doses of 20 – 30 mg/m² of body-surface area for at least 24 months
4. to evaluate the efficacy and side-effects of adding etanercept, a novel antirheumatic drug, to prevailing drug therapy for a one-year period in children with JIA refractory to conventional DMARDs
5. to estimate the costs of adding etanercept to prevailing drug therapy for a one-year period in children with JIA whose disease has proved refractory to conventional DMARDs

4. Patients and methods

4.1. Patients

Demographics and patient characteristics of the patients in the individual studies (I-V) are presented in the following table (Table 3): All patients fulfilled the Durban criteria for JIA.

Studies	Number of patients	Sex (female/male) N	Age at onset mean (SD)	Onset type N
I	32	27/5	9.1 (2,8)	Oligoarthritis 10 Polyarthritis 19 Systemic 3
II	74	NA	NA	NA
III	34	26/8	11.5 (3,0)	Oligoarthritis 8 Polyarthritis 23 Systemic 3
IV and V	31	22/9	9.6 (range 3 – 15)	Oligoarthritis 6 Polyarthritis 22 Systemic 3

4.1.1. CyA in JIA (I)

In 32 children with active JIA resistant to conventional DMARD therapy, which in all cases included MTX, the prevailing treatment was intensified by adding CyA 2.5-3 mg/kg/day. The mean age of the patients was 9.1 (SD 2.8) years. Fourteen had uveitis at the onset of CyA. Half of the patients continued on CyA for at least two years.

The effect of CyA treatment was analysed retrospectively from the medical records. The treatment effect was assessed by the change in hospitalization days, dose of peroral prednisolone, i.a. glucocorticoid injections, and change in erythrocyte sedimentation rate (ESR) and serum concentration of C-reactive protein (CRP).

4.1.2. Serum MTX concentration and HCQ (II)

Of 105 consecutive JIA patients treated at the RFH and receiving MTX treatment, 74 were included in this study. They were divided into three groups according to MTX dose: 10, 20 and 30 mg/square meter/week. Numbers of patients in these groups also receiving HCQ were 13 out of 27, 17 out of 36, and 4 out of 11, respectively. The daily dose of HCQ was approximately 5 mg/kg.

4.1.3. Hepatotoxicity of methotrexate (III)

Transcutaneous liver biopsies were taken during 1992-1997 from all patients receiving long-term (more than 2.4 years) MTX therapy and followed up by our hospital. The first 34 patients with JIA were included in the study.

4.1.4. Etanercept in JIA (IV)

A total of 31 patients with severe JIA resistant to conventional DMARDs and 27 also resistant to MTX were selected for this study. These patients represent the most severe and treatment-resistant cases in the whole country. Their mean age was 9.6 years (range from 3 to 15). Twelve patients had uveitis.

Etanercept was added to the prevailing treatment at a dose of 0.4 mg/kg of body weight twice a week. Previous treatment (Table 4) was continued until inflammatory activity was markedly reduced or remission was attained. Outcome variables were peroral prednisolon dose, DMARD therapy, intra-articular glucocorticoid injections, ESR and serum concentration of CRP.

4.1.5. Costs of etanercept therapy (V)

The patients included in this study were the same as in (IV).

4.2. Methods

4.2.1. Determination of MTX concentration (II)

MTX was administered before lunch (standard hospital food without any dairy products). Blood samples were taken 90 minutes after intake of MTX. MTX concentrations were determined by fluorescence polarization immunoassay technology (TDX; Abbott, Abbott Park, IL). Interassay variance ranged from 5.1% to 7.3%.

4.2.2. Liver biopsy and histological examination (III)

Liver biopsies were taken under local anesthesia or general anesthesia given for intra-articular injections during scheduled inpatient visits to the hospital. Altogether 24 initial and 5 follow-up biopsies were carried out by the same person (JH). No complications occurred. Histological changes in the biopsy specimens were combined for grading by the Roenigk classification (Roenigk et al. 1982).

4.2.3. Assessment of costs (V)

Direct and indirect costs were retrospectively collected from medical records and complemented by parental inquiry, and are expressed here as medians. Direct costs were collected over an 18-month period, comprising a 6-month pre-treatment period and a 12-month period with etanercept. The average 3-month costs were calculated for the 6 months' pre-treatment period, and these were used as reference costs. After the initiation of etanercept, three-month sequencing was used to even out the effect of variation in disease activity and treatment on the costs. Of pharmacological expenditures other than the costs of etanercept, only the costs of DMARDs were considered. For these drugs, pharmacy prices were used, taking into account package size. In the case of the i.a. glucocorticoid injections, only the costs related to general anesthesia were taken into account.

Indirect costs were taken to include losses in work input of the parents and travel costs excluding VAT. Losses of work input were calculated using the

weighted gross earnings of men and women plus employer's non-wage costs. The costs of losses of work input due to children's hospitalization were considered only for the days on which parental presence was necessary for treatment. Parent's accommodation costs were not taken into account. Parent's losses of work input due to visits to laboratory and physiotherapy were not considered, since they could be arranged mainly outside parents' profitable working hours. The computations give average prices for each cost heading (median cost) per patient over three months. Computational costs of treatment of JIA are shown in Table 5.

4.2.4. Statistical analysis

Study I. The data were assessed by intention-to-treat analysis after two years from the onset of CyA. The last observation carried forward was used in cases of missing clinical or laboratory data. The statistical significance of the observed differences was analysed by Kornbrot's rank difference test.

Study II. Differences in MTX concentrations between subjects with and without HCQ were calculated by t-test with Hommel's modification of the Bonferroni procedure.

Study III. Correlations of liver histology with MTX doses or with elevations of liver enzymes were analysed by Fischer's exact test. The relationship between cumulative MTX doses and the histological score was analysed by permutation test.

Study IV. Analysis of efficacy was based on intention-to-treat analysis with the last observation carried forward. Statistical comparison of changes in outcome measures was made using Kornbrot's rank difference test and the Friedman two-way analysis of variance by ranks.

Study V. Due to their skewed distribution, cost data are presented as medians with interquartile rate. No sensitive analysis was made, since the expenses considered were not based on assumptions. Assessment of the effect of etanercept treatment on the costs was based on a comparison of median costs of a three-month pre-treatment period and those of the last three months of the treatment period. These data were projected for one

year, respectively to obtain the annual change in costs during etanercept treatment. The significance of the change was determined by permutation tests with general scores with Monte Carlo p-values. Bonferroni adjustments were used to correct significance levels for multiple testing.

5. Results

5.1. Combining CyA with prevailing treatment (I)

Both ESR and CRP showed a significant reduction during the two years' follow-up period ($p < 0.05$ and < 0.001 , respectively) (Table 6). Other outcome measures did not improve. One patient with polyarthritis achieved a remission which lasted up to the two-year check-up. In two patients uveitis healed completely and in six others uveitis improved initially, but the change was restricted to the first six months.

Side-effects were frequent, but usually mild and reversible and did not incur cessation of treatment in any case.

5.2. Serum concentration of MTX and HCQ (II)

MTX concentrations were correlated to the MTX dose/m². Concomitant use of HCQ had no significant effect on MTX serum concentrations in patients with JIA (Figure 1).

5.3. Hepatotoxicity of MTX (III)

All liver specimens from 24 patients with MTX of < 20 mg / square meter/week were classified normal grade I. Of the 10 patients with MTX doses 20 mg/square meter/week or more, four had grade II and five had grade I histological changes, while one specimen with extensive steatosis as the only pathological finding could not be classified. No specimen showed fibrosis or cirrhosis. In two patients with grade II histological changes, extensive portal tract inflammation resolved when MTX was

discontinued for six months. Serum transaminase levels did not correlate with liver histology.

There was a positive correlation between grade II histology and high MTX dose ($p < 0.01$). High cumulative MTX doses also had a significant association with grade II histology ($p < 0.01$). In the four patients with a grade II histology, the median cumulative dose was 4 250 mg, whereas in those with grade I histology the median cumulative dose was 1 600 mg. Elevated liver enzymes at any time during MTX therapy were not associated with grade II histology ($p = 0.63$).

5.4. Combining etanercept with the prevailing treatment (IV)

The beneficial effect of etanercept was already seen at the three months' control (Table 7). After 12 months there were significant improvements in the daily prednisolon dose ($p < 0.001$), in the number of DMARDs used ($p < 0.001$), in the number of necessary intra-articular glucocorticoid injections ($p < 0.001$), in ESR ($p = 0.001$), and in the serum CRP concentration ($p = 0.012$). These effects remained stable during the follow-up period. In addition, there was a marked decrease in the number of hospitalization days from the 3-month period before etanercept to the last 3-month period during etanercept (medians 8 and 3, respectively).

No clear effect was found on the course of the eye disease in the 12 patients with uveitis at baseline. Two out of these 12 experienced an activation of uveitis during the follow-up.

Etanercept was well tolerated. Two patients had recurrent urticaria-like reactions after etanercept injections, which necessitated cessation of treatment after three weeks in one, and after four months in the other. In two patients treatment was discontinued because of inefficacy and in one case etanercept was changed to infliximab because of difficulties in carrying out the injections at home.

5.5. Costs of etanercept (V)

The total costs per patient were estimated for a three-month period before the initiation of etanercept therapy and during the one-year follow-up. Results are presented in Table 8. When the costs attributable to etanercept were excluded, the change in the median direct costs was -54% (approximately - 10 000 US dollars per patient on the annual level). This was due mainly to a reduction in treatment days and use of DMARDs. On the annual level, the total direct costs rose by 4 220 US dollars per patient ($p=0.006$). Indirect costs dropped by 50% during the follow-up period ($p=0.005$), i.e. by 1 688 US dollars per child in one year. This means a saving of approximately 10-14 work days per escorting parent per year. The total median costs rose by 2 716 US dollars (+10%) as estimated on an annual level ($p=0.09$).

6. Discussion

6.1 General

JIA is often a benign and transient disease which has no detrimental effects on the long-term outcome of the child. It can, however, be a ferocious and cruel condition leading to severe disability, dwarfism, blindness and even death. Such outcomes are not only catastrophic for the individual concerned, but a serious and expensive burden for the whole society.

The etiology of JIA is not known, and no curative treatment is available. The several disease types of JIA may have different etiologies, and each of these should have its specific curative treatment method. For the same reason primary prevention is not possible. The best feasible strategy is secondary prevention, which requires early finding of cases and effective treatment before permanent destruction of joints.

It would be desirable to have reliable prognostic signs or markers in the early stages of JIA in order to select treatment according to the probable

future development. Unfortunately no such markers are available (Adib et al. 2005, II). All incipient cases should therefore be considered as potential disabled patients. This means that all patients should be treated in the best possible way from the beginning of the disease.

All drugs used in children with JIA come from adult rheumatology. The mechanism of therapeutic action in the older drugs is not known, and very few of them have been properly investigated in JIA. With the exception of MTX and other cytotoxic drugs the evidence basis for the effectiveness of therapies for JIA patients is weak, and no one therapy stands out as the first choice once MTX has failed (Cummins et al. 2002). Only from the beginning of this millennium have biological drugs, particularly anti-TNF agents, offered new therapeutic strategies, and even these are not perfect. There are non-responders, the drugs may have adverse effects, and they do not cure the disease. At best, however, they very effectively suppress the inflammatory activity and can prevent the progression of the disease.

It will be interesting to see, whether ongoing studies of the polymorphisms in genes encoding TNF-alpha, TNF-alpha receptors, other cytokines, and the major histocompatibility complex region will offer means to predict the response to anti-TNF therapies in children with JIA (Ranganathan 2005).

Drugs are an important part of the comprehensive treatment programme in JIA, but only one part. Before the advent of today's effective therapies severe deformities and disabilities were common (Vainio 1956): orthopedic surgery was the only means of ameliorating the condition. Surgery was also used as an anti-inflammatory strategy in the form of synovectomies. Removal of inflammatory tissue from a joint was considered to reduce inflammation at least locally, but possibly also in general. Results of surgical synovectomies in JIA are not, however, particularly convincing.

Growth of bone close to an active inflammatory focus leads to disturbances. The growth plates can be destroyed, and bone growth ceases. This can take place especially in the small joints of fingers or toes

and in the cervical spine. Micrognathia was earlier a typical sign of chronic JIA in consequence of delayed growth of the mandibula. No effective treatment is available for the cessation of bone growth.

In the knee joints acceleration of growth is common, probably due to the elevated temperature resultant upon local inflammation. This can lead to valgus deformity and/or leg length discrepancies. These deformities can be successfully treated by temporary surgical stapling of the epiphyses (Skyttä et al. 2005).

Active inflammation in the complicated joint areas of the wrist and ankle can lead to marked deformities. Guidance of bone growth with external splints corrected at regular intervals, has in fact given satisfactory results.

Orthopedic surgery, orthoses and splints retain a place in the treatment programme, but their relative importance has declined considerably with the development of drug treatment.

6.2 Structure of trials in the present study

Randomized controlled clinical trials provide the best means of distinguishing a drug from placebo without the inevitable selection biases are seen in standard clinical care. The primary design in clinical trials is a parallel, in which patients are randomized in parallel to different therapies at different dosages, or to placebo. In recent years, other designs have been used to an increasing extent, including "step-up," "step-down," and "cross-over" designs. Limitations of clinical trials in chronic diseases include the short time frame of the trial versus the long duration of the disease, inclusion and exclusion criteria, use of surrogate markers which may not represent clinically relevant markers. Statistical significance does not necessarily indicate clinical significance, and the use of a control group does not assure freedom from bias (Pincus and Sokka 2004).

Our JIA patient population is rather small, which means difficulties in organizing randomized controlled studies on DMARDs or biologicals. The patients in the present series represent a real clinical material. The case selection was based on evaluation of patients treated on the same clinical grounds, e.g., patients with a given cumulative MTX dose in studies considering liver biopsy (study III) and with or without concomitant HCQ therapy (study II), or refractory JIA not responding to traditional DMARD therapy (studies I and IV).

The present studies of the efficacy of CyA and etanercept were uncontrolled and retrospective. The long-term follow-up of the patients, however, allowed us to use pre-treatment data as control. Change in clinical findings after inclusion of a new drug in the prevailing treatment was, indeed, very clear in the case of etanercept; the therapeutic power of the drug could be demonstrated without a control group.

Our practice is always to treat JIA by i.a. glucocorticoid injections, when clinical signs of active synovitis are present. Injections are repeated at consecutive hospital visits if clinical or ultrasound-based activity is found. The number of joint injections can thus be used as a measure in swollen joint count. Measuring ESR and CRP is routinely used at inpatient visits. The health assessment questionnaire for children (CHAQ) is not in routine use at our hospital, and was therefore not available in these retrospective studies.

6.3 Results

According to the present series, combination of CyA with the prevailing DMARD treatment, which included MTX in all cases, has only a marginal antiarthritic effect (I). However, the results support the usefulness of this strategy in the treatment of uveitis. CyA has been used fairly successfully in the treatment of uveitis together with glucocorticoids and MTX (Kotaniemi 1998). In ocular Behcet's disease it is currently one of the most effective drugs (Ozdal et al. 2002).

It has been reported that simultaneous administration of chloroquine reduces the bioavailability of MTX in adult patients with RA (Seideman et al. 1994). In children chloroquine is not used, but combination of HCQ with MTX is common. It is possible that HCQ prevents the side-effects of MTX (Möttönen et al. 1999), one possible explanation for this protective effect being the low serum concentration of MTX if simultaneous HCQ is used (Seideman et al. 1994). The present study (II) quite clearly demonstrated, however, that simultaneous HCQ does not lower the serum concentrations of MTX. Theoretically, HCQ could increase the serum level of MTX through its inhibitory effect on aldehyde oxidase, which metabolizes MTX to less active metabolites. In fact, our results show rather an increase than a decrease in MTX concentration in children receiving simultaneous HCQ.

The liver biopsies in the series were carried out between the years 1992–1997. The hepatotoxicity of MTX is well documented. Liver fibrosis or cirrhosis has been reported in adults with idiopathic arthritis receiving MTX (Brick et al. 1989). In children with JIA, neither cirrhosis nor severe fibrosis has been found, but a few cases of mild fibrosis have been reported (Keim et al. 1990, Hashkes et al. 1999). According to this series (III), histological changes are mild and reversible also after a large cumulative dose. However, liver toxicity is a potential side-effect of MTX, and monitoring of the serum liver enzymes is mandatory. According to the present results liver biopsies are not necessary in the routine follow-up of patients with JIA.

The clinical efficacy of etanercept in refractory JIA could be demonstrated (study IV). The need for other drugs, DMARDs as well as oral and intra-articular glucocorticoids declined. On the other hand, there were treatment failures and in two patients adverse effects necessitated withdrawal of the drug. In addition, etanercept seemed not to have favourable effect on uveitis.

JIA presents with a wide variety of disease severity. Some patients can be treated with non-steroidal anti-inflammatory drugs only, or the disease can even be cured without any medications. It is evident that MTX is an effective second-line drug for patients not responding to NSAIDs. Some patients, however, do not tolerate MTX or respond adequately to it. In these cases other DMARDs or combinations of them are often tried. Such patients are likely to experience substantial morbidity persisting into adult life, with a serious impact on their quality of life. They also often need increasing amounts of hospital treatment. As shown in the present series, hospital days have constituted the most expensive item in the direct costs of JIA.

JIA is a potentially fatal or permanently disabling disease, which, however, can be successfully treated. The costs may be high in the case of biological agents, but the prevention of permanent disability in children yields such savings and benefits not only to the patient, but also to society, that an effective therapy is almost never too expensive. The decision-makers, however, need information regarding the costs and benefits of these expensive drugs.

In the present economic evaluation of the costs of etanercept (study V), expenses were included only when they could be unambiguously attributed to the treatment of JIA. Other costs, especially indirect, were intentionally excluded. Here the costs were calculated over a period of 12 months, which can be considered long enough in view of the clinical outcome and cost calculations. It is plausible that the greatest cost reductions will take place thereafter. Long-term follow-up of biologicals is required for a better estimation of reduction in comorbid conditions, orthopedic surgery and mortality, and also the relative risk of adverse effects (Solomon and Maetzel 2004).

This study included the therapeutic introduction of a new drug, etanercept, in Finland. This raised the monitoring costs at the beginning of treatment. It is to be noted that the costs of etanercept therapy are lower today than

at the time when this study was conducted, since with increasing clinical experience treatment can now be given on an outpatient basis.

It is to be noted that the present study was conducted in Finland, where the therapeutic approach in JIA may be different compared to other parts of the world. Our protocol includes active use of DMARDs and i.a. glucocorticosteroids, and the baseline situation of the patients when the drug interventions (studies I-II and IV-V) were started may thus be fundamentally different from that in countries where the cornerstone of therapy is NSAIDs. The results are therefore not necessarily applicable to overall pediatric rheumatological practice.

7. Conclusions

Based on studies I-V it may be concluded that

- during combination of CyA with prevailing treatment in severe JIA ESR and CRP improved significantly, but no effect could be seen in glucocorticoid dose or hospitalization days;
- contrary to an earlier report concerning RA, simultaneous HCQ did not reduce the bioavailability of MTX in patients with JIA;
- at doses below 20 mg/body-surface square meter weekly, MTX does not cause pathological changes in liver tissue samples. No irreversible changes were seen at higher doses, although in four out of ten patients minor changes were seen;
- the novel antirheumatic drug etanercept is highly effective in the treatment of refractory JIA. In only two out of 31 patients had the drug to be discontinued for lack of efficacy;
- etanercept increases the total costs by 2 716 US dollars, i.e. 10% per patient per year. This must be viewed against the background of reduced inflammatory activity in the joint disease and the probable reduction of lifetime pain and disability produced by the disease.

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Table 4. Data on baseline drugs used by patients (study IV)

Therapy	N (%)
Drugs:	
Hydroxychloroquine	14 (45)
Cyclosporin	21 (68)
Injectable gold	4 (13)
Azathioprine	12 (39)
Sulphasalazine	2 (6)
Methotrexate	27 (87)
Podophyllotoxin	2 (6)
Prednisolone (every 2nd day)	30 (97)
Strategy:	
No drugs	0 (0)
DMARD alone	0 (0)
One DMARD with prednisolone	3 (10)
Prednisolone alone	0 (0)
DMARD combination	1 (3)
DMARD combination with prednisolone	27 (87)

Table 5. Computational unit costs of treatment of JIA (study V).

Treatment and examination services	Price \$
Inpatient ward therapy at RFH (one day)	405
Visit to outpatient department	20
General anesthesia for joint injections	235
Physiotherapy*:	
Therapy at health center	42
Therapist's visit at home	101
Laboratory visit*	10
Visit to a nurse*	13
(administration of methotrexate- etanercept injections)	

RFH = Rheumatism Foundation Hospital

*Ref. Heikkinen et al. 2001

Table 6. Outcome in 32 JIA patients after adding cyclosporine to the prevailing DMARD treatment (study I)

Variable	Baseline Median (IQR)	At 24 months Median (IQR)	Median change ⁴ Median (95% CI)	p-value ⁵
Hospitalization days ¹	5.5 (4.0 , 7.5)	9 (4 , 15)	4 (0.5 to 7.0)	0.040
Prdn, dose, mg ²	10.0 (7.5 , 15.0)	10 (7.5 , 17.0)	0 (-2.5 to 2.5)	0.82
GC injections ³ , n	3 (1.5 , 5.0)	4.5 (2 , 8)	2 (0.5 to 4.0)	0.022
ESR, mm/h	36 (18 , 52)	20 (12 , 36)	-10 (-1.5 to -22.0)	0.012
CRP, mg/l	27 (5 , 71)	2 (0 , 12)	-28 (-8.0 to -40.5)	<0.001
fS-urea mg/l	3.8 (3.2 , 4.6)	4.2 (3.6 , 5.5)	0.5 (-1.0 to 1.2)	0.088

² Every other day. ¹ and ³ Calculated within 3-month periods. ⁴ Rank-based confidence interval for difference in paired medians. ⁵ Kornbrot's rank difference test. IQR = interquartile rate

Table 7. Improvement according to individual outcome variables. Intention-to-treat analysis with LOCF. (study IV)

Variable	Baseline Median (IQR)	End point Median (IQR)	Median change ³ Median (95% CI)	p-value ⁴
Prdn, dose ¹ , mg	12.5 (10.0-20.0)	7.5 (5.0-15.0)	-5.0 (-2.5 to -7.5)	<0.001
DMARDs, n	3 (2-3)	2 (1-2)	-1 (-0.5 to -1.0)	<0.001
GC injections ² , n	8 (3-11)	1 (0-3)	-6 (-3 to -9)	<0.001
ESR, mm/h	34 (19-53)	17 (8-32)	-15 (-8 to -21)	0.001
CRP, mg/l	8 (6-35)	0 (0-11)	-8 (-2 to -18)	0.012

¹ Dose of prednisolone every 2nd day.

² Calculated within 3-month periods.

³ Rank-based confidence interval for difference in paired medians.

⁴ Kornbrot's rank difference test.

Upper normal limits for ESR and CRP are 12 mm/h and 10 mg/l, respectively.

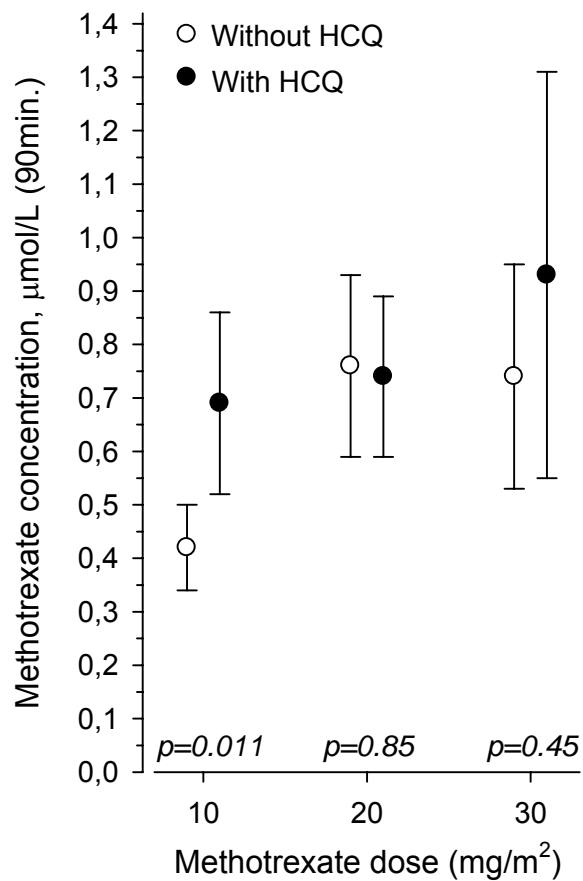
Table 8. Costs of treatment of juvenile rheumatoid arthritis during one-year therapy with etanercept. Costs (\$) are given as medians and quartile intervals (study II).

Costs	Before start (/3mo) Median (IQR)	Enbrel® therapy			
		0-3 months Median (IQR)	3-6 months Median (IQR)	6-9 months Median (IQR)	9-12 months Median (IQR)
Direct:					
Treatment ¹	3448 (2243 , 4252)	3046 (1640 , 3850)	1841 (1439 , 3046)	1607 (804 , 2644)	1439 (804 , 2644)
Medication	417 (187 , 693)	265 (93 , 689)	139 (65 , 237)	122 (65 , 210)	81 (65 , 236)
Enbrel® therapy	0	3804	3804	3804	3804
Physiotherapy	1000 (1000 , 1000)	1000 (1000 , 1000)	1000 (875 , 1000)	1000 (875 , 1000)	1000 (875 , 1000)
Laboratory ²	39 (10 , 39)	29 (19 , 48)	19 (17 , 48)	19 (15 , 29)	19 (19 , 27)
Other ³	724 (407 , 1122)	764 (492 , 1067)	649 (465 , 1087)	598 (448 , 936)	590 (465 , 872)
Indirect:					
Transportation to school	0 (0 , 42)	0 (0 , 0)	0 (0 , 0)	0 (0 , 0)	0 (0 , 0)
Loss of working time	696 (557 , 1253)	557 (278 , 1113)	348 (278 , 731)	418 (278 , 696)	348 (278 , 418)
Total:					
Direct	6284 (4671 , 7245)	9056 (7573 , 9962)	7320 (6873 , 9476)	7204 (6730 , 8854)	7339 (6099 , 8340)
Indirect	840 (696 , 1253)	557 (278 , 1113)	487 (278 , 772)	554 (278 , 721)	418 (278 , 645)
Grand total	7053 (5545 , 8459)	9807 (7795 , 10908)	7740 (7116 , 10260)	7892 (7078 , 9606)	7732 (6377 , 8955)

¹ Inpatient ward, outpatient clinic and general anesthesia related to injection costs.

² Visits for safety laboratory tests when at home. Does not concern the inpatient period or visits to the outpatient clinic.

³ Includes travel costs and costs related to the administration of injections (methotrexate and etanercept)



Serum methotrexate concentrations in patients with juvenile idiopathic arthritis who were and those who were not receiving hydroxychloroquine (HCQ). P-values were calculated using t-test with Hommel's modification of the Bonferroni procedure.

10. Original communications

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Combining cyclosporine with prevailing antirheumatic drug therapy in the treatment of juvenile idiopathic arthritis

Sirs,

The effect of cyclosporine either alone or in combination with various disease modifying antirheumatic drugs (DMARD), mainly methotrexate, has been shown in rheumatoid arthritis (1). However, there is little data on the effect of cyclosporin in the treatment of juvenile idiopathic arthritis (JIA) and they have mainly focused on the systemic onset type of the disease (2). There are no studies which have assessed the effect of a combination of cyclosporine with other DMARDs in JIA. We retrospectively analysed the usefulness of adding cyclosporine to the treatment protocol in 32 children (27 girls and 5 boys) with active JIA resistant to conventional DMARD therapy, which in all cases included methotrexate. The mean (SD) age of the patients was 9.1 (± 2.8) years. The onset type of the disease was: extended oligoarthritis (n=6), oligoarthritis (n=4), polyarthritis (n=19) and systemic onset JIA (n=3). Fourteen patients had iritis at the onset of cyclosporine treat-

ment.

After the onset of cyclosporine treatment most patients continued to use their earlier DMARD combination including methotrexate in every case. Cyclosporine plus methotrexate was combined with two other DMARDs in 6 patients, with one DMARD in 16 patients, and 10 patients had a simple cyclosporine plus methotrexate combination. The drugs in the combinations were methotrexate (n=32), natrium aureothioma-late (n=2), sulfasalazine (n=8), hydroxy-chloroquine (n=17), and azathioprine (n=1). The prevailing drug therapy remained stable, and we did not include in this analysis patients in whom the DMARD therapy had been changed. At the onset of cyclosporine treatment, the mean starting dose of methotrexate was 20.1 mg/week in the 14 patients who used it *per os* and 21.4 mg in the 18 patients who received it parenterally. The mean initiating dose of cyclosporine was 2.5-3 mg/kg/day. Sixteen (50%) out of the 32 patients took cyclosporine for at least two years. Side effects were monitored following good clinical practice with special attention devoted to blood pressure and renal function, measured by the level of serum urea, and by the creatinine clearance test in cases with a suspicion of impaired renal function.

For this study the effect of treatment and the side effects were checked from the medical records up to 2 years from the onset of the treatment. The treatment effect was assessed as a change in hospitalisation days and in prednisolone dose, and by the common inflammatory indexes, i.e. the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Our treatment policy includes treating all clinically active joints with intra-articular corticosteroids. Thus, for this retrospective study we also considered the change in the number of active joints as an outcome measure of disease activity. The data were assessed by intention-to-treat (ITT) analysis after to years from the onset of cyclosporine treatment.

The last observation carried forward (LOCF) was used when there were missing clinical and laboratory data.

Table I shows our main results. Both ESR and CRP showed a significant reduction, while there was a significant increase in the need for hospitalisation and for intra-articular corticosteroid injections. One patient with polyarthritis had a remission after 6 months which lasted up to the two-year check-up. Side effects were frequent but usually mild or reversible, and did not require in any case the cessation of the therapy. In 2 cases with iritis the signs of inflammation totally disappeared; in one of them, however, the follow-up had lasted only one year. In addition, 6 patients initially showed improvement in their iritis, but this was restricted to the first 6-month period.

In conclusion, this series represented active, severe cases of JIA who were aggressively treated with various DMARD combinations without achieving disease control. In all cases we added cyclosporine to the prevailing drug therapy which included methotrexate. After adding cyclosporine to the prevailing DMARD combination there was a significant reduction in laboratory indexes of inflammation. On the other hand, there was an increase in the number of intra-articular corticosteroid injections needed and in the number of hospitalisation days. Moreover, spontaneous fluctuations in different factors that represent disease activity can modify the result. Overall our results are based on retrospective data and must be considered preliminary. Though all of the patients had methotrexate and cyclosporine as a minimum combination, 2/3 of the patients in the series had additional DMARDs which invalidizes the analysis as to a given drug combination. Mild side effects were frequent, but adverse effects were not seen. We are awaiting controlled studies on this important topic.

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Table I. Outcome in 32 JIA patients after adding cyclosporine to the prevailing DMARD treatment.

Variable	Baseline Median (IQR)	At 24 months Median (IQR)	Median change ³ Median (95% CI)	p-value ⁴
Hospitalisation days ¹	5.5 (4.0, 7.5)	9 (4, 15)	4 (0.5 to 7.0)	0.040
Prdn, dose, mg ²	10.0 (7.5, 15.0)	10 (7.5, 17.0)	0 (-2.5 to 2.5)	0.82
GC injections ¹ , n	3 (1.5, 5.0)	4.5 (2, 8)	2 (0.5 to 4.0)	0.022
ESR, mm/h	36 (18, 52)	20 (12, 36)	-10 (-1.5 to -22.0)	0.012
CRP, mg/l	27 (5, 71)	2 (0, 12)	-28 (-8.0 to -40.5)	< 0.001
fS-urea mg/l	3.8 (3.2, 4.6)	4.2 (3.6, 5.5)	0.5 (-1.0 to 1.2)	0.088

¹Calculated within 3-month periods; ²Every other day; ³Rank-based confidence interval for difference in paired medians; ⁴Kornbrot's rank difference test. IQR = interquartile range.

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Hepatotoxicity in Patients with Juvenile Idiopathic Arthritis Receiving Longterm Methotrexate Therapy

PEKKA LAHDENNE, JUHANI RAPOLA, HEIKKI YLIJOKI, and JARKKO HAAPASAARI

ABSTRACT. Objective. To evaluate hepatotoxicity in patients with juvenile idiopathic arthritis (JIA) receiving methotrexate (MTX) therapy with doses of 20–30 mg/m² of body surface area.

Methods. We graded the histology of percutaneous liver biopsies from 34 patients with JIA receiving longterm (> 2.4 years) MTX therapy at the Rheumatism Foundation Hospital, Heinola, Finland, using the Roenigk classification scale. Medical records of the patients with JIA were retrospectively analyzed.

Results. Of 10 patients with MTX doses \geq 20 mg/m², 4 had grade II, 5 had grade I histology, and one specimen with extensive steatosis as the only pathologic finding could not be classified. All 24 patients treated with low dose MTX had grade I histology. No specimen showed fibrosis or cirrhosis. In 2 patients with grade II histology, extensive portal tract inflammation resolved when MTX was discontinued for 6 months.

Conclusion. Aggressive medical treatment of JIA with MTX at 20–30 mg/m² with concomitant disease modifying antirheumatic drugs and corticosteroids may contribute to minor liver abnormalities that seem to be reversible. (J Rheumatol 2002;29:2442–5)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS

METHOTREXATE

HEPATOTOXICITY

Low dose (10 mg/m² of body surface area) weekly methotrexate (MTX) has been established as an effective treatment for children with juvenile idiopathic arthritis (JIA)^{1,2}. In patients with unsatisfactory responses to a low dose, MTX doses of 15 or 20 mg/m² given orally once a week have shown efficacy in short term treatment for extended oligoarticular and systemic JIA^{3,4}. However, not all patients benefit from this treatment and higher doses of MTX are frequently used in patients with severe unremitting polyarticular or systemic JIA^{5–7}. The efficacy of MTX at higher doses has not been established in a randomized, controlled fashion, nor has the tolerability.

One potential side effect of MTX is hepatotoxicity. Liver fibrosis or cirrhosis has been reported in adults with idiopathic arthritis receiving MTX therapy^{8–10}. In pediatric JIA series, neither cirrhosis nor severe liver fibrosis has been found^{11–15}, but a few cases of mild fibrosis have been reported^{15–17}. The low dose MTX therapy does not seem to be associated with severe hepatotoxicity^{11–15}. However, with increasing use of antirheumatic treatments with higher doses of MTX and combinations of disease modifying antirheumatic drugs (DMARD), it is now necessary to pay

critical attention not only to the efficacy but also to the safety issues.

We evaluated hepatotoxicity in patients with JIA receiving longterm MTX therapy in combination with DMARD. In particular, the effects of high (\geq 20 mg/m²) weekly doses of MTX on liver histology were investigated in detail.

MATERIALS AND METHODS

Study subjects. The medical records of patients with JIA followed at the Rheumatism Foundation Hospital, Heinola, Finland, were reviewed. Between 1992 and 1997, we performed a percutaneous liver biopsy for all patients receiving longterm (> 2.4 years) MTX therapy. Thirty-four patients with JIA, 26 girls and 8 boys, were included in the study (Table 1). All patients fulfilled the Durban criteria for JIA¹⁸. No patient had psoriatic arthritis. Alcohol consumption was assessed by personal interview of the patients over 14 years of age. No hints indicative of alcohol consumption were observed. No patient had diabetes mellitus. During the course of the disease, all patients had taken nonsteroidal antiinflammatory drugs (NSAID) but not on the same day as MTX. Liver enzyme tests were routinely performed every 4 to 6 weeks one or 2 days before the next weekly MTX dose. Elevated levels > 2.5 times the upper limit of normal range had been recorded.

Liver biopsies. We performed liver biopsies under general anesthesia given for intraarticular injections during scheduled inpatient visits at the Rheumatism Foundation Hospital. All biopsies were done by one of 2 authors (JH or HY) with a Hepafix G17 (Medical Braun) needle. After formalin fixation, the biopsy specimens were embedded in paraffin wax, sectioned at 5 μ m, and stained with hematoxylin and eosin. Informed consent was obtained from all the patients and/or parents.

Assessment of histologic grade. Pertinent histologic findings were scored as follows: Fat: 0 = no fat, 1 = occasional fatty cells, 2 = 1–10% fatty cells in the specimen, 3 = > 10% fatty cells in the specimen. Portal inflammation: 0 = none, 1 = small number of inflammatory cells in some portal tracts, 2 = inflammation in all portal tracts, 3 = extensive portal tract inflammation.

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Table 1. Characteristics of the 34 patients with JIA receiving longterm methotrexate (MTX) therapy.

	Mean ± SD or Number	Range
Age, yrs	11.5 ± 3.0	6.2–18.0
Duration of JIA, yr	8.2 ± 3.0	3.2–15.3
Duration of MTX therapy, yr	4.5 ± 1.7	2.4–9.8
Concomitant use of NSAID	11	
Steroid	22	
DMARD	21	
Other cytotoxic drugs	4	
Sex		
Female	26	
Male	8	
Disease onset mode		
Systemic	3	
Polyarticular	23	
Oligoarticular	8	
Disease course		
Polyarticular	34	
Antinuclear antibodies	8	
Rheumatoid factor	0	
HLA-B27	9	

Nuclear variability (anisonucleosis): 0 = none, 1 = mild to moderate, 2 = marked. Fibrosis: 0 = none, 1 = thin and short radiating septa, 2 = extensive fibrosis. The changes in the biopsy specimens were combined for grading by the Roenigk classification¹⁹. The histologic review with scoring and grading was done by one author (JR) without knowledge of the patient's identity or clinical history.

Statistical analysis. Correlations of liver histology with MTX doses or with elevations of liver enzymes were analyzed with Fisher's exact test. The relationship between cumulative MTX doses and the histologic score was analyzed with the permutation test.

RESULTS

Indications for liver biopsy. Altogether, 34 initial and 5 followup biopsies were performed. Two patients with MTX therapy of long duration (over 7 years) had initial biopsies after 3 years of MTX use and followup biopsies 4 years

later. Two patients with extensive portal inflammation in the initial biopsies (Patients 3 and 4 in Table 2) had one or 2 followup biopsies 6 months after discontinuation of MTX.

Medical treatment. In all 34 patients, MTX was initially started with a 10 mg/m² dose orally. In cases of continued inflammatory activity, the MTX dose was escalated. Doses over 20 mg/m² were given subcutaneously. Ten patients had been treated with 20–30 mg/m² MTX weekly for 6 to 36 months prior to the biopsy (Table 2). In these patients, the total duration of MTX therapy was 30 to 84 months (mean 54 mo, median 58 mo), and the cumulative dose ranged from 1300 to 6200 mg (mean ± 1 SD, 3470 ± 1632 mg, median 3600 mg). At the time of the biopsy, all 10 patients were receiving DMARD and 9 of them were taking alternate day prednisolone. Six of the 10 were receiving NSAID (Table 2). During the study period, folate or folic acid was not used on a regular basis for patients taking MTX.

During MTX treatment, of the 10 patients with > 20 mg/m² MTX or 24 patients with low dose MTX, 4 (40%) or 10 (42%), respectively, had elevated liver enzymes > 2.5 times the upper limit of normal range.

Histopathologic findings in liver biopsies. Liver biopsies from all 24 patients with low dose MTX were classified grade I. Of the 10 patients with > 20 mg/m² of MTX, 5 had grade I, 4 had grade II liver biopsy, and in one specimen the only pathologic change was extensive steatosis, and therefore it could not be classified according to the Roenigk scale. This specimen came from an overweight patient (Patient 8, Table 2) whose body mass index (BMI) was 33.8 (kg/m²). No specimen showed fibrosis or cirrhosis.

In 2 cases with > 20 mg/m² MTX doses, portal inflammation was moderate to severe (Patients 3 and 4 in Table 2). In both specimens, > 10% of the specimen consisted of fatty cells. Patient 4 had been treated with MTX for over 6 years prior to the biopsy, and parenterally 30 mg/m² for the preceding 6 months. In the followup biopsies of both

Table 2. Drug treatment and liver biopsy findings in 10 patients with JIA receiving high dose MTX therapy.

Patient	Patient Age, yrs	MTX CD, mg	Duration of MTX, mo	Current Dose of MTX, mg/m ²	Concomitant use of			Histological Findings				
					Steroid*	DMARD	NSAID	Anisonucleosis 0–2	Portal Inflammation 0–3	Fat 0–3	Fibrosis 0–2	Grade (Roenigk)
1	9.5	1300	36	22	10	HQ	Naproxen	1	0	1	0	I
2	8.4	1500	37	27.5	5	HQ	No	1	1	1	0	I
3	9.8	1900	30	20	0	ATM	No	1	2	3	0	II
4	13.5	6200	84	30	10	ATM	No	0	3	3	0	II
5	8.8	3100	58	30	7.5	AZA	Diclofenac	1	0	2	0	II
6	18	4500	66	20	5	HQ	Naproxen	1	1	1	0	I
7	14.2	5400	64	30	20	HQ	Ketoprofen	1	1	2	0	II
8	7.7	4100	65	25	15	HQ	Naproxen	0	0	3	0	UC
9	9.7	3100	44	20	2.5	HQ	Naproxen	1	0	1	0	I
10	6.2	3600	54	30	5	ATM	No	1	0	1	0	I

*Steroid dose is alternate day dose of prednisolone. CD: cumulative dose, DMARD: disease modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug; HQ: hydroxychloroquine; AZA: azathioprine; ATM: intramuscular aurathiomalate; UC: unclassifiable (this case showed extensive steatosis as the only pathologic change).

patients, when MTX was discontinued for 6 months the portal inflammation resolved.

Statistical analysis. MTX doses > 20 mg/m² were correlated with grade II histology of the liver biopsies (Fisher's exact test, $p = 0.003$). Higher cumulative MTX doses were also associated with grade II histologic score (permutation test with exact 2 sided $p = 0.005$). In the 4 patients with grade II histology, the median cumulative MTX dose was 4250 mg, whereas in the patients with grade I histology, the median cumulative MTX dose was 1600 mg. Elevated liver enzymes > 2.5 times the upper limit of normal range any time during MTX treatment were not associated with the histologic grade (Fisher's exact test, $p = 0.63$). One of the 4 patients with grade II liver histology had highly elevated transaminases.

DISCUSSION

Our study provides for the first time an analysis of the liver histology in patients with JIA treated with high doses of MTX (> 20 mg/m²), and allows insights into the possible hepatotoxicity of this treatment. This retrospective study provides evidence that higher MTX doses may increase the risk for histopathologic liver changes. However, these changes seem to be reversible, because regardless of high doses of MTX, cumulative doses up to 6 g, and the use of MTX in combination with other DMARD, we did not find any case of fibrosis or cirrhosis.

The 10 patients treated with higher doses of MTX represent patients with prolonged polyarticular disease course. All patients were treated with various combinations of DMARD and oral and intraarticular corticosteroids. Steatosis was a common finding in many liver biopsies. It is possible that longterm use of corticosteroids and active inflammatory disease *per se* may also have contributed to the liver changes. However, resolution of portal inflammation in 2 patients when MTX was discontinued support the idea that MTX contributed to the liver changes. It has been suggested that concurrent use of hydroxychloroquine might protect the liver against MTX toxicity²⁰. The limited numbers of patients taking various combination therapies and the absence of fibrosis preclude any meaningful statistical evaluation of hepatotoxicity. Thus, we were unable to show protective effects or additive toxicities in patients receiving DMARD. Because folic acid was not used at the time of the study, the putative hepatoprotective effects of this drug²¹ could not be assessed either.

Currently, it is not known whether minor liver changes in patients with JIA treated with MTX would progress to significant histopathology later in life. In sequential liver biopsies of adult patients with idiopathic arthritis during MTX therapy, results regarding the progression of fibrosis have been conflicting²². Most probably, other confounding factors, e.g. alcohol use, preexisting liver disease, and obesity, especially when associated with diabetes mellitus,

may contribute to hepatotoxicity. Such factors were not evident in our series, except for mild to moderate obesity in a small number of patients (data not shown). Obesity is also recognized as a contributing factor to the development of hepatic steatosis that frequently progresses to liver fibrosis²³. However, there are no reports on MTX causing extensive hepatic steatosis. Thus, most probably, in one patient in this study obesity was the major factor in the development of hepatic steatosis. In 7 other patients with moderate obesity in our series, no significant liver abnormalities were observed (data not shown).

Retrospective studies of patients with JIA have shown that short term hepatic toxicity (transaminase elevations) does not occur more frequently with higher than with low dose MTX treatment⁵⁻⁷. These findings do not, however, exclude the possibility of longterm hepatotoxicity due to MTX treatment because single abnormal transaminase levels may not be sensitive markers for significant hepatotoxicity. A recent study suggested that serial liver enzyme abnormalities in JIA patients taking MTX therapy might be associated with histopathologic liver changes¹⁵. Due to the retrospective nature of our study, the frequency of elevated transaminases could not be accurately assessed. Because serial liver enzyme abnormalities might reflect recurrent hepatocyte damage and result in formation of scar tissue and fibrosis, Hashkes, *et al*¹⁵ suggested that biopsy should be considered for patients with JIA if 40% or more of the biochemical liver tests were abnormal in the course of a year.

Our results support the consensus that liver biopsies merely because of longterm MTX therapy are not indicated, and that the potential for severe hepatotoxicity of low dose MTX is minimal in JIA^{11-15,24}. However, our results also imply that treatment of JIA with high doses of MTX with DMARD and corticosteroids may contribute to portal inflammation and steatosis of the liver, changes that are potential risk factors for liver fibrosis. Larger prospective studies are needed to define the appropriate guidelines for monitoring of patients with JIA receiving aggressive antirheumatic drug therapy.

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Good results from combining etanercept to prevailing DMARD therapy in refractory juvenile idiopathic arthritis

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Key words: Juvenile idiopathic arthritis, arthritis, juvenile rheumatoid, anti-TNF therapy, combination therapy, biological agents

ABSTRACT

Objective. To assess the effect of etanercept added to prevailing drug therapy in patients with juvenile idiopathic arthritis (JIA) whose disease was refractory to conventional disease-modifying antirheumatic drug (DMARD) treatment, including combinations of different DMARDs.

Methods. Data on 31 JIA patients with a disease resistant to conventional DMARD treatment were retrospectively collected from medical records and assessed for a one-year period after the introduction of etanercept or to the time of cessation of the drug due to a lack of efficacy or side effects. Efficacy was assessed based on the normal laboratory indexes of inflammation and changes in the following parameters: number of DMARDs used and intra-articular (i.a.) glucocorticoid injections. The numbers of inpatient days needed were also recorded.

Results. Etanercept was well tolerated. Only two patients stopped discontinued the treatment because of allergic rash, after 3 weeks of treatment in one case and after 4 months in another. In two cases the treatment was discontinued because of a lack of efficacy. During the treatment, there was a significant decrease in the number of DMARDs used and the i.a. glucocorticoid injections needed as well as in the dose of per oral glucocorticoids. The laboratory parameters also improved. In addition, there was a significant decrease in the number of inpatient days per 3-month period before and during the etanercept treatment.

Conclusion. The addition of etanercept to conventional DMARD therapy in children with the most severe cases of JIA leads to an excellent clinical response during the first 12 months. The tolerability of the drug is good in combination therapy with various DMARDs.

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous disease with a spectrum from pauciarticular non-deforming disease to polyarticular destructive disease prone to severe manifestations, such as amyloidosis, need for total joint re-

placement surgery, osteoporosis and retarded growth (1). Though the prognosis seems now better than some decades ago, especially thanks to more active use of methotrexate (mtx), there are still cases resistant to conventional disease-modifying antirheumatic drug (DMARD) therapy. In such instances, tumor necrosis factor (TNF)-blockers may be useful.

Etanercept is a biologic response modifier that binds the cytokines TNF and lymphotoxin- α , thus blocking their interaction with cell-surface receptors (2). Etanercept is a genetically engineered fusion protein consisting of two p75-soluble TNF receptor molecules fused to the Fc fragment of human immunoglobulin G₁.

There are scant published data on the clinical use of etanercept in JIA. A two-part, multicenter trial of etanercept in children with active polyarticular juvenile rheumatoid arthritis (JRA) refractory or intolerant to mtx therapy reported etanercept to be effective and well tolerated (3). The patients represented all of the three major onset types. In the first part of the study, where all patients received open-label etanercept at 0.4 mg/kg subcutaneously twice weekly for 90 days, 74% achieved the JRA definition of improvement. In the double-blind part of the study, where the responders were randomized to either placebo or etanercept, a significant difference was seen in the disease flare frequency between the groups, with percentages of 81% and 28%, respectively. There were no significant differences between the two treatment groups in the frequency of adverse reactions, injection site reactions being most common in the active group.

We have three years' experience of the clinical use of etanercept in the treatment of JIA. The results reported here are retrospective data on the effect and safety of the compound in the treatment of active JIA refractory to conventional drug treatment. Our treatment schedule was to use etanercept in combination with the prevailing DMARD therapy.

Patients and methods

According to the statistics of the

Finnish Social Insurance Institute, the total number of children with JIA is approximately 1,200 in the population of about one million children in Finland. The care of patients with JIA in Finland is strongly centralised to the Rheumatism Foundation Hospital (RFH), which means that almost all severe cases of JIA in the country are under our supervision.

Since the spring of 1999, there has been a possibility to receive etanercept in Finland. At that time, the first children with the most severe JIA were chosen for the treatment. There is a total of 31 JIA patients who have started etanercept treatment between April 1999 and September 2000 in our hospital. We report retrospectively collected data on the results of the therapy.

The series consisted of 23 girls and 8 boys. The mean age at the start of the treatment was 9.9 years (range 3 - 15) and the duration of the disease was 6.4 (range 0.8 - 13.6) years. The commonest diagnosis was polyarthritis (in 22 children), while 6 patients had extended oligoarthritis and 3 systemic onset disease (Table I).

The mean number of current DMARDs used was 2.6 (range 1 - 4). All patients had received mtx during their disease course, and 26 patients were still taking it at the beginning of the study. The maximum dose of mtx

Table I. Baseline demographic and clinical characteristics of 31 patients with JIA.

Characteristics	
Sex:	
Girls, n (%)	22 (71)
Boys, n (%)	9 (29)
Mean age (range), years	9.6 (3 - 15)
Diagnosis	
Extended oligoarthritis, n (%)	6 * (19)
Seronegative polyarthritis, n (%)	22 (71)
Systemic onset disease, n (%)	3 (10)
Mean disease duration (range), years	6.3 (0.8 - 13.6)
Number of patients with uveitis (%)	12 (39)

*One patient had antinuclear antibody-positivity.

was 30 mg/m²/week. The mean dose of *per oral* corticosteroid was 16 (range 0 - 40) mg of prednisolone every other day. All the patients continued their earlier treatment (Table II) until inflammatory activity was strongly reduced or remission was attained. Thereafter, the conventional treatment was gradually reduced.

The mean number of i.a. corticosteroid injections calculated from the 3-month period before the introduction of etan-

Table II. Data on the baseline drugs of the patients.

Therapy	No. (%)
Drugs:	
Hydroxychloroquine	14 (45)
Cyclosporin	21 (68)
Injectable gold	4 (13)
Azathioprine	12 (39)
Sulphasalazine	2 (6)
Methotrexate	27 (87)
Podophyllotoxin	2 (6)
Prednisolone (every 2nd day)	30 (97)
Strategy:	
No drugs	0 (0)
DMARD alone	0 (0)
One DMARD with prednisolone	3 (10)
Prednisolone alone	0 (0)
DMARD combination	1 (3)
DMARD combination with prednisolone	27 (87)

cept was 8. During the study, glucocorticoid injections were given at the routine hospital visits or between them if necessary, and for this retrospective analysis, the number of i.a. injections needed was recorded as an indicator of treatment effect (4).

At the baseline of the etanercept treatment, all patients had active disease. The mean erythrocyte sedimentation rate (ESR) was 40 mm/h and the mean C-reactive protein (CRP) was 25 mg/l (Fig. 1).

The patients received etanercept with a standard dose of 0.4 mg/kg of body weight twice a week. They were seen in the RFH paediatric ward by a paediatric rheumatologist at least every three months. The standard laboratory tests, i.e., ESR, CRP, blood count, liver enzymes and fS-urea were made at every hospital visit.

Statistical analysis

The analysis of the efficacy of treatment was based on an intention-to-treat (ITT) analysis with the last observation carried forward (LOCF). A statistical comparison of the changes in the outcome measurements was performed by using Kornbrot's rank difference test and the Friedman two-way analysis of variance by ranks. The most important descriptive values were expressed with a rank-based 95% confidence interval (CI) for difference in paired medians. The level was set at 0.05 for all tests.

Results

Etanercept was well tolerated. Two patients had recurrent urticaria-like reactions after the etanercept injections, which necessitated cessation of the treatment after three weeks in one case and after four months in another (5). Some other patients had minor side effects, which did not, however, necessitate cessation of the treatment. The drug was discontinued in two patients due to inefficacy, after three months in one and after six months in another. In addition, one patient was admitted to another hospital nearby her place of residence after 9 months' follow-up. Furthermore in one patient the treatment was changed to infliximab after four months due to difficulties to carry out the etanercept injections at home.

The beneficial effect of etanercept on the activity of the disease was already seen at the 3 months' control (Fig. 1). The median value of ESR (mm/h) and that of CRP (mg/l) decreased from 34 to 14 and from 13 to 1, respectively. During the same period, it was possible to cut down the median dosage of *per oral* corticosteroids equivalent to prednisolone every second day from 10 to 7.5 mg. Overall six patients were able to stop corticosteroids during the trial. The median (95% confidence interval) change in the number of DMARDs during the follow-up was -1 (-0.5 to -1.0). Mtx dose could be decreased in eight patients by a mean of 5 mg, from 25 to 20 mg. The median number of i.a. corticosteroid injections per 3 months was reduced from 8 to 1 injections. These beneficial effects were stable

during the follow-up period of 12 months (Table III). In addition, there was a marked decrease in the number of hospitalisation days assessed from the consecutive 3-month periods before the start of the therapy to the end of the follow-up (median 8.0 and 3.0, respectively).

No clear-cut effect was found on the course of the eye disease in the 12 patients with uveitis. Two patients out of the 12 experienced an activation of their uveitis during the follow-up.

Discussion

The present series included the most severe cases of JIA. All the patients had been treated with several DMARDs and with different drug combinations without achieving acceptable disease control. Against that background, the effect of etanercept on the outcome measurements used – laboratory indexes of inflammation, number of i.a. glucocorticoid injections given and inpatient days needed was excellent, with statistically significant improvements during the follow-up. Due to our active treatment policy, the number of i.a. glucocorticoid injections in this retrospective series can be considered as comparable to the number of swollen joints (4). During the one-year follow-up, there was also a clear trend towards a reduction of the number of DMARDs and the dose of per oral corticosteroids needed.

In addition to the efficacy of etanercept in this clinical series, it is to be noted that no serious side effects were seen, though we added the compound to the prevailing DMARD drug therapy.

There are some reports on the improv-

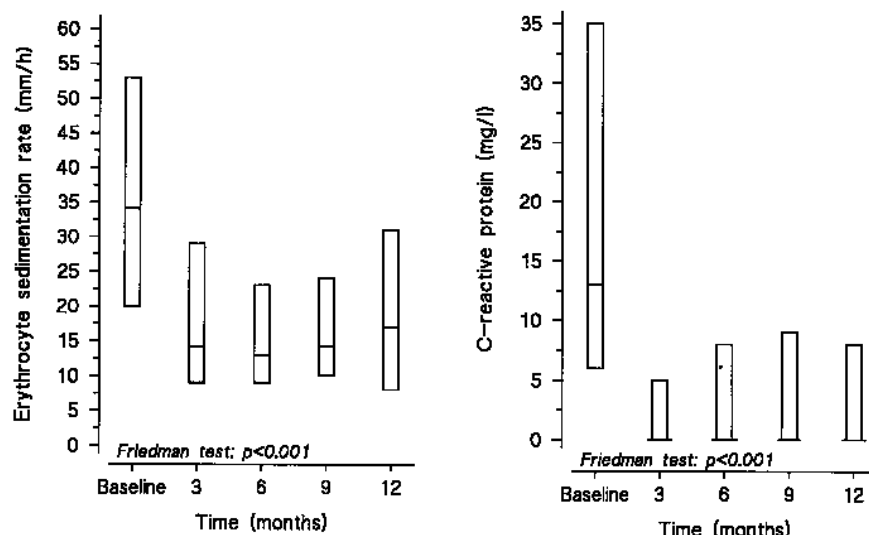


Fig. 1. Treatment response estimated by ESR and CRP during a follow-up of 12 months in 31 JIA patients. In the box plot model, the horizontal line in the middle of the bar represents median and the lower and upper boundaries the 25th and 75th percentiles, respectively. Upper normal limits for ESR and CRP are 12 mm/h and 10 mg/l, respectively.

ing outcome of JIA during the last decade including our own experience (6). The result can be speculated to be due to an increasing use of cytostatic drugs. Nowadays there is a consensus to treat JIA aggressively, with mtx up to a weekly dose of 30 mg/m² as the gold standard, a schedule which has shown satisfactory results in 60-80% of patients (7). However, there are still cases whose disease cannot be controlled with conventional DMARDs. In such instances, which made up our present series, etanercept is the drug of choice (8).

It is to be noted that the mean disease duration in our series was over 6 years, which means that many of our patients with active disease had been waiting for an effective drug for years. In such

cases, it is naturally optimal to start TNF blockers earlier in the disease course.

In conclusion, according to our present retrospective analysis, combination of etanercept to the prevailing DMARD treatment seems well-tolerated and effective for patients with JIA resistant to conventional therapy

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Table III. Improvement according to individual outcome variables. Intent-to-treat analysis with LOCF.

Variable	Baseline Median (IQR)	End point Median (IQR)	Median change ³ Median (95% CI)	p-value ⁴
Prdn, dose ¹ , mg	12.5 (10.0-20.0)	7.5 (5.0-15.0)	-5.0 (-2.5 to -7.5)	< 0.001
DMARDs, n	3 (2-3)	2 (1-2)	-1 (-0.5 to -1.0)	< 0.001
GC injections ² , n	8 (3-11)	1 (0-3)	-6 (-3 to -9)	< 0.001
ESR, mm/h	34 (19-53)	17 (8-32)	-15 (-8 to -21)	0.001
CRP, mg/l	8 (6-35)	0 (0-11)	-8 (-2 to -18)	0.012

¹Dose of prednisolone every 2nd day; ²calculated within 3-month periods; ³rank-based confidence interval for difference in paired medians; ⁴Kombrot's rank difference test.

Upper normal limits for ESR and CRP are 12 mm/h and 10 mg/l, respectively.

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Etanercept Does Not Essentially Increase the Total Costs of the Treatment of Refractory Juvenile Idiopathic Arthritis

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ABSTRACT. Objective. To assess the costs of adding etanercept to the prevailing drug therapy for a one-year period in a group of 31 children with juvenile idiopathic arthritis (JIA) whose disease was refractory to conventional disease modifying antirheumatic drugs.

Methods. The changes in total costs were retrospectively collected from medical records and by interviewing parents 6 months before the initiation of etanercept treatment and during a 12-month followup divided into 3-month periods.

Results. Direct median costs increased during the first 3 months after the introduction of etanercept, but decreased later during the followup. The estimated median direct costs per patient increased by US \$4200 per year, and the indirect costs were reduced by 50%, i.e., \$1700. The estimated median total cost per patient was increased by about \$2700 per year (10%).

Conclusion. After combining etanercept with the prevailing treatment, the total costs of refractory JIA calculated per year were only slightly higher than those of traditional therapy. This finding must be evaluated in light of the reduced inflammatory activity of the joint disease and the probable reduction of lifetime pain and disability produced by the disease. (*J Rheumatol* 2004;31:2286–9)

Key Indexing Terms:

ETANERCEPT
REFRACTORY

TREATMENT COSTS
JUVENILE IDIOPATHIC ARTHRITIS

Longterm disability is the main cause of the burden imposed by musculoskeletal diseases. Although the prevalence of juvenile idiopathic arthritis (JIA) is low, patients will suffer from the disease throughout their adult life¹. Thus, in the most severe cases, the impact of the disease on both the individual and society is considerable¹. There are recent reports about improvement of the outcome of JIA^{2,3}, including our own experience². This can be attributed to the increasing use of cytostatic drugs and intraarticular treatments. Currently there is a consensus to treat JIA aggressively with methotrexate (MTX) as the gold standard⁴, with satisfactory results in 60–80% of patients⁵. According to the results of recent randomized controlled trials, higher doses (up to a dose of 15–20 mg/m² body surface area weekly) of MTX than those conventionally used (8–12.5 mg/m²) improve efficacy^{6,7}. However, there are still cases whose disease cannot be controlled with conventional disease modifying antirheumatic drugs (DMARD). In such instances, which made up our present series, etanercept is the drug of choice⁸.

A positive effect of etanercept (Enbrel[®]), a recombinant tumor necrosis factor receptor, on the disease activity of

patients with JIA was reported in one randomized controlled trial^{9,10}. In addition, a few observational studies have documented substantial efficacy of etanercept when combined with DMARD^{11–14}; only 2 of the series included followup for one year or longer^{13,14}. There are no studies on the health-economic aspect of etanercept therapy in JIA¹⁰.

We have reported retrospective one-year data on the clinical effect of etanercept in 31 patients with JIA whose disease was refractory to conventional DMARD therapy¹⁴. In conclusion, after combining etanercept with the prevailing therapy, a positive treatment effect was documented in the form of statistically significant reductions in the laboratory indicators of inflammation, in the dose of oral corticosteroids, in the number of intraarticular steroid injections needed, and in the number of inpatient days.

We now report the total costs of this treatment schedule of JIA during a one-year period from this same series and compare them with the total costs of an average of 3 months from a 6-month pretreatment period.

MATERIALS AND METHODS

According to statistics from the Finnish Social Insurance Institute, the total number of children with JIA is roughly 1200 in the population of about one million children in Finland. The care of patients with JIA in Finland has been strongly centralized to the Rheumatism Foundation Hospital (RFH), which means that almost all severe cases of JIA in the country are under our supervision. It has been possible to use etanercept medication in Finland since the spring of 1999. At that time, the first children with the most severe JIA were chosen for treatment. Altogether 31 patients with JIA started etanercept between April 1999 and September 2000 in our hospital.

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Demographic data and disease characteristics of the 31 patients have been reported¹⁴. Briefly, 6 had extended oligoarthritis, 22 had polyarthritis, and 3 systemic onset JIA. The patients' mean age was 10 years (range 3–15) and mean disease duration 6 years (range 1–14). At the time of starting etanercept, 28 (90%) patients were receiving a combination of 2 or more DMARD and 3 patients one DMARD. All except one patient had systemic corticosteroid therapy, with a mean (range) dose of prednisolone 16.3 (0–45) mg every 2nd day. All patients continued their earlier treatment until inflammatory activity was strongly reduced or remission was attained. The followup was organized by the Paediatric Department of RFH. Routine clinical and laboratory tests were used to monitor the safety of the drug, and patients' physiotherapy programs were continued, as determined earlier, during the observation period. Intraarticular corticosteroid injections were given (often under general anesthesia) whenever inflamed joints were detected.

Cost data collection. Direct and indirect costs were retrospectively collected from medical records and complemented by parental inquiry, and they are expressed as medians.

Direct costs. The data for economic evaluation were collected over an 18-month period, including a 6-month pretreatment period and a 12-month treatment period with etanercept. The average 3-month costs were calculated for the 6 months' pretreatment period, and these were used as reference costs. After the initiation of etanercept, 3-month sequencing was used to even out the effect of variation in disease activity and treatment on the costs. Table 1 shows the unit costs used for the calculation of direct costs. Only costs considered to be directly related to arthritis were included.

Of pharmaceutical expenditures other than the cost of etanercept, only the costs of DMARD were considered. For these drugs, pharmacy prices were used, taking package size into account. The costs of nonsteroidal anti-inflammatory drug (NSAID) use were not included in the analysis because the retrospective study design and the use of these drugs "as necessary" would have made the calculations unreliable. For the intraarticular corticosteroid injections, only costs related to general anesthesia were taken into account; other costs, such as those due to laboratory testing and physiotherapy, were included in the hospital fee. The costs due to the latter procedures outside RFH are also shown in Table 1.

Indirect costs. Travel expenses related to arthritis were calculated on the basis of the medical certificates addressed to the Social Insurance Institution, where the need for special transportation is documented. Reimbursement of \$0.35 per kilometer was calculated for using one's own car. For transportation by taxi, train, bus, and plane, the price excluding tax was calculated as the cost. The costs related to transportation to school by taxi based on the medical certificate were also considered. Indirect costs mainly consisted of computational losses of work by the children's parents, which were calculated using the weighted gross earnings of men and women plus the employer's non-wage costs, taking into account the unemployment rate of men and women and their employment. The calculated daily price was \$137 in 1999 and \$142 in 2000 (all costs US dollars). The costs of losses of work input due to children's hospitalization were considered only for the days on which parental presence was necessary for treat-

Table 1. Computational unit costs of treatment of JIA.

Treatment and examination services	Price, \$
Inpatient ward therapy (one day)	405
Visit at outpatient department	20
General anesthesia for joint injections	235
Physiotherapy ¹⁶	
Therapy at health center	42
Therapist's visit at home	101
Laboratory visit ¹⁶	10
Visit to a nurse ¹⁶ (administration of methotrexate-etanercept injections)	13

ment. Parents' accommodation costs were not taken into account. Parents' losses of work time due to visits to the laboratory and physiotherapy were not considered, because they could mainly be organized outside the parents' profitable working hours. The computations give average prices for each cost heading (median cost) per patient in periods of 3 months.

Etanercept therapy. Etanercept was administered subcutaneously twice weekly. The wholesale price excluding tax for 4 injections of the preparation, \$640, was taken as the price. Calculation of costs of administering etanercept injections was based on the assumption that the injection was given by the school nurse or a nurse in the nearest health center, and it was considered as an additional cost of \$13.

Statistical methods. Due to their skewed distribution, cost data are presented as medians with an interquartile rate (IQR). No sensitivity analysis was done, because the expenses considered were not based on assumptions. Assessment of the effect of etanercept treatment on the costs was based on the comparison of median costs of a 3-month pretreatment period (estimated from 6 months before etanercept treatment) and those of the last 3 months of the treatment period. These data were projected for one year, respectively, to have an annual change of costs during etanercept treatment. The significance of the change was determined by permutation tests with general scores with Monte Carlo p values. Bonferroni adjustments were used to correct significance levels for multiple testing.

RESULTS

The total costs per patient estimated for a 3-month period before the initiation of etanercept therapy and during the one-year followup are presented in Table 2. When the costs due to etanercept are excluded, the change in the median direct costs was -54% (approximately -\$10,000 per patient on an annual basis), which was mainly due to the reduction of treatment days and use of DMARD. Estimated on an annual level, the total direct costs rose by \$4220 per patient ($p = 0.006$). Indirect costs dropped by 50% during the followup period ($p = 0.005$), i.e., \$1688 per child in one year. This means a saving of about 10–14 work days per escorting parent per year. The total median costs rose by \$2716 (+10%) estimated on an annual basis ($p = 0.09$).

DISCUSSION

The main aim of the treatment of JIA is to suppress inflammation and to prevent longterm disability. If this target cannot be reached, chronic arthritis inevitably leads to joint destruction and a loss of function and disability. JIA is associated with growth inhibition, loss of vision (as a result of uveitis), and a significant risk of premature death due to infections, myocarditis, or the side effects of drugs and, in certain populations, amyloidosis¹. Alleviation of inflammation by optimal treatment, if it could be developed, would inhibit these manifestations. Economic benefits would be obtained by preventing life-long disability and incapacity.

To our knowledge, this is the first cost-consequence analysis of etanercept therapy in JIA. Assessment of health economics is important in a real clinical setting, such as ours. The rise of overall median costs during etanercept therapy per child per year in this patient series consisting of the most severe forms of juvenile rheumatoid arthritis was only about \$2700 (a rise of 10%). The major part of the drop in direct costs was caused by the reduced need for treatment

Table 2. Costs of treatment of juvenile rheumatoid arthritis during one-year therapy with etanercept (Enbrel). Costs (\$) are given as medians (interquartile range).

Costs	Etanercept Therapy				
	Before start (/3mo)	0–3 mo	3–6 mo	6–9 mo	9–12 mo
Direct					
Treatment*	3448 (2243, 4252)	3046 (1640, 3850)	1841 (1439, 3046)	1607 (804, 2644)	1439 (804, 2644)
Medication	417 (187, 693)	265 (93, 689)	139 (65, 237)	122 (65, 210)	81 (65, 236)
Etanercept therapy	0	3804	3804	3804	3804
Physiotherapy	1000 (1000, 1000)	1000 (1000, 1000)	1000 (875, 1000)	1000 (875, 1000)	1000 (875, 1000)
Laboratory**	39 (10, 39)	29 (19, 48)	19 (17, 48)	19 (15, 29)	19 (19, 27)
Other †	724 (407, 1122)	764 (492, 1067)	649 (465, 1087)	598 (448, 936)	590 (465, 872)
Indirect					
Transportation to school	0 (0, 42)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Loss of working time	696 (557, 1253)	557 (278, 1113)	348 (278, 731)	418 (278, 696)	348 (278, 418)
Subtotal					
Direct	6284 (4671, 7245)	9056 (7573, 9962)	7320 (6873, 9476)	7204 (6730, 8854)	7339 (6099, 8340)
Indirect	840 (696, 1253)	557 (278, 1113)	487 (278, 772)	554 (278, 721)	418 (278, 645)
Total	7053 (5545, 8459)	9807 (7795, 10908)	7740 (7116, 10260)	7892 (7078, 9606)	7732 (6377, 8955)

* Inpatient ward, outpatient clinic, and general anesthesia related to injection costs. ** Visits for safety laboratory tests when at home. Does not concern the inpatient period or visits to the outpatient clinic. † Includes travel costs and costs related to the administration of injections (methotrexate and etanercept).

days, which was reflected positively in the costs of the parents' work input, implying savings of 10–14 work days per child per year.

In our series, costs were calculated only when they could be unambiguously attributed to the treatment of JIA. Other costs, especially indirect ones, were intentionally excluded. Costs were calculated over a period of 12 months, which can be considered long enough in view of the clinical outcome and the cost calculations. It is plausible that the greatest cost reductions would continue after that.

This study included the therapeutic introduction of a new drug in Finland. That made the monitoring costs higher at the beginning of the treatment. It should be noted that the costs of etanercept therapy are lower today than they were when this study was conducted. With increasing clinical experience, the treatment can be given at home today.

Conventional drugs, especially MTX, have recently yielded fairly good therapeutic results, most patients with JIA being able to live almost without restrictions. In a few patients, however, the disease is refractory and development of disability cannot be prevented. The need for new drugs is greatest in these unresponsive patients. About 2.5% of children with JIA in Finland were actively recruited into this series. They represent the individuals most severely affected by JIA, and all had also been treated with MTX and different drug combinations. The number of children to be treated was mainly restricted by the availability of etanercept. According to the latest information¹⁵, roughly 15% of all those with JIA will die or become disabled for work, which means about 180 children in Finland. This would

apparently be the maximum number of patients who could be treated with the new biological medicines in line with current principles. It is possible that the principles of treatment of JIA will change in such a way that even more patients will be able to receive biological antiinflammatory drugs at an even earlier stage of the disease course. The problem remains how to predict the patients with a poor prognosis early enough.

This study was done in Finland, where therapeutic approaches to JIA may be different compared to other parts of the world, including North America. Our protocol includes active use of DMARD and intraarticular corticosteroids, and NSAID are used only as necessary, in contrast to the practice of using NSAID as the cornerstone of therapy. In addition, our practice of hospitalizing patients, first to facilitate proper multidisciplinary care and second due to long distances, may not be relevant in other parts of the world such as North America. Although our series represents the cases with the most severe JIA in Finland at the time of study, the center-specific treatment approaches and patient selection criteria may have influenced the results of the study, with an influence on its external validity. Therefore, as in any economic analysis, the results may not be generalizable to other healthcare systems.

It can be concluded that the addition of etanercept to the prevailing treatment did not increase the overall costs compared to conventional therapy. This must be viewed against the background of the reduced inflammatory activity and the probable reduction of lifetime pain and disability produced by the disease.

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