Anti-TNF Treatment in Juvenile Idiopathic Arthritis and Associated Uveitis

Clinical Perspectives on Growth, Uveitis, and Drug Survival

Pirjo Tynjälä

ACADEMIC DISSERTATION

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Abstract

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of childhood chronic arthritides that is associated with chronic uveitis in 20% of cases. Approximately 20-30% of patients respond inadequately to conventional disease-modifying anti-rheumatic drugs (DMARDs). During the last decade new medicinal products, biologic agents, have become available for these refractory patients. Among biologic therapies, anti-tumor necrosis factor (anti-TNF) agents etanercept, infliximab, and adalimumab are in current use for children.

We conducted a multicenter study on growth in 71 patients refractory to DMARDs, who started etanercept or infliximab treatment before age 15 and had never taken growth hormone. Growth was reviewed for 2 years prior to initiation of anti-TNF therapy and for 2 years after treatment commenced. Records showed that 53 patients (75%) had delayed and 18 patients (25%) normal or accelerated growth velocity prior to initiation of anti-TNF agents. Measured as a change in a height standard deviation score (ΔHSDS), 53 patients with delayed growth demonstrated a significant increase in growth velocity after initiation of anti-TNF agents. In them, the mean annual increase in growth velocity was +0.45 [95% confidence interval (CI) 0.33 to 0.56, p<0.001] ΔHSDS. In 18 patients with normal growth, ΔHSDS was +0.05 (95% CI -0.07 to 0.16, p=0.390). After two years of anti-TNF therapy, growth rate in the 53 patients had caught up to that of the 18 patients. The increase in growth rate was unrelated to pubertal growth spurt, and also in prepubertal patients growth was enhanced. No change was observed in skeletal maturation before and after anti-TNF therapy. The strongest predictor of change in growth velocity was growth rate prior to anti-TNF therapy. The change in inflammatory activity remained a significant predictor even after the decrease in glucocorticoids was taken into account. Patients were able to significantly reduce their use of glucocorticoids and DMARDs, and at the final visit 52% had inactive rheumatic disease.

In JIA-associated uveitis, we evaluated the impact of two first-line biologic agents, etanercept and infliximab, and second-line or third-line anti-TNF agent, adalimumab, on anterior chamber (AC) inflammation. Ocular inflammatory activity was graded according to the number of AC cells, and improvement in uveitis was measured as reduced number of AC cells. In a retrospectively reviewed cohort of 108 refractory JIA patients, uveitis occurred in 45 patients (42%), of whom 24 were on etanercept and 21 on infliximab. The endpoint ophthalmologic evaluation was at 24 months or at termination of the first biologic agent. Of the 45 patients, uveitis improved in 14 (31%), no change was observed in 14 (31%), and in 17 (38%) uveitis worsened. Uveitis improved more frequently (p=0.047) in patients on infliximab than in those on etanercept (43% and 21%, respectively). The frequency of annual uveitis flares was higher (p<0.015) in those on etanercept (mean 1.4, range 0-3.2) than in those on infliximab (mean 0.7, range 0-2.0). The first phase of uveitis occurred during anti-TNF therapy in 5 patients: 4 on etanercept (2.2/100 patient-years) and 1 on infliximab (1.1/100 patient-years).

In addition, we reviewed records of 20 patients with JIA-associated uveitis taking adalimumab, of whom 17 (85%) had polyarticular JIA and 19 (95%) had previously failed etanercept and/or infliximab. The mean duration of adalimumab therapy was 18.7 months. Of the 20 patients, in 7 (35%) uveitis improved, in one (5%) worsened, and in 12 (60%) no
change occurred. Those with improved uveitis were younger and had shorter disease duration. During adalimumab treatment the mean number of annual uveitis flares decreased from 1.9 to 1.4. Serious adverse events (AEs) or side-effects were not observed. Adalimumab seemed to be effective also in most patients with active arthritis. In arthritis symptoms, American College of Rheumatology Pediatric 30% (ACR Pedi30) improvement was observed at 3 months in 64% of 14 patients, at 6 months in 57% of 14 patients, at 12 months in 60% of 10 patients, at 18 months in 83% of 6 patients and at 24 months in 100% of 6 patients, respectively.

In a multicenter follow-up study of JIA patients starting anti-TNF therapy before age 16, we evaluated long-term drug survival (i.e. continuation rate on drug) during 1999-2007 and predictors of treatment discontinuation. Of the 209 patients, 105 were taking etanercept and 104 infliximab. Drug survival with etanercept vs. infliximab therapy was at 12 months 83% vs. 80%, at 24 months 68% vs. 68%, at 36 months 64% vs. 53%, and at 48 months 61% vs. 48%, respectively (p=0.194 in log-rank analysis). The first-line anti-TNF agent was discontinued either due to inefficacy (etanercept 28% vs. infliximab 20%, p=0.445), AEs (7% vs. 22%, p=0.002), or inactive disease (10% vs. 16%, p=0.068). Females, patients with systemic JIA (sJIA), and those taking infliximab as the first therapy were at higher risk (assessed as hazard ratios) for treatment discontinuation. One-third of patients switched to the second anti-TNF agent, which was discontinued less often than the first. During the second-line anti-TNF treatment, 12-month drug survival on etanercept was 60%, on infliximab 58%, and on adalimumab 66%.

In conclusion, in the treatment of refractory JIA, TNFα blockers induced enhanced growth velocity in patients with growth delay, which was probably due to reduction in inflammatory activity rather than a direct effect on growth plates or on skeletal maturation. During etanercept or infliximab treatment, ophthalmologic condition of one-third of patients with JIA-associated anterior uveitis improved, and infliximab seemed to be more effective than etanercept in reducing inflammatory activity of uveitis. Adalimumab was beneficial in one-third of JIA patients with chronic anterior uveitis and provided a potential treatment option even for patients non-responsive to first-line anti-TNF agents. The four-year treatment survival on anti-TNF agents was high and comparable between etanercept and infliximab, although infliximab was discontinued more often than etanercept due to adverse events. In JIA, a switch from the first-line anti-TNF agent to the second-line agent appears to be a reasonable therapeutic option.
Acknowledgments

This study was carried out during 2003-2007 at the Hospital for Children and Adolescents, University of Helsinki, and at the Rheumatism Foundation Hospital, Heinola, in collaboration with the Department of Ophthalmology, University of Helsinki, and the Department of Pediatrics, University of Oulu.

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Helsinki, August 2008

Pirjo Tynjälä
List of original publications

This thesis is based on the following publications, which are referred to in the text by Roman numerals I-IV:


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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AC</td>
<td>Anterior chamber (of eye)</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ACR20</td>
<td>20% improvement in ACR criteria</td>
</tr>
<tr>
<td>ACR Pedi30</td>
<td>30% improvement in ACR Pediatric criteria</td>
</tr>
<tr>
<td>ANA</td>
<td>Antinuclear antibodies</td>
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<tr>
<td>BCVA</td>
<td>Best-corrected visual acuity</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CHAQ</td>
<td>Childhood Health Assessment Questionnaire</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CSA</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>DAS</td>
<td>Disease Activity Score</td>
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<tr>
<td>ΔHSDS</td>
<td>Change in Height Standard Deviation Score</td>
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<tr>
<td>DMARD</td>
<td>Disease-Modifying Anti-Rheumatic Drug</td>
</tr>
<tr>
<td>ERA</td>
<td>Enthesitis related arthritis</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<tr>
<td>GH</td>
<td>Growth hormone</td>
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<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HSDS</td>
<td>Height Standard Deviation Score</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
</tr>
<tr>
<td>ILAR</td>
<td>International League of Associations of Rheumatology</td>
</tr>
<tr>
<td>iv</td>
<td>Intravenous</td>
</tr>
<tr>
<td>JCA</td>
<td>Juvenile chronic arthritis</td>
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<tr>
<td>JIA</td>
<td>Juvenile idiopathic arthritis</td>
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<tr>
<td>JRA</td>
<td>Juvenile rheumatoid arthritis</td>
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<tr>
<td>JSPA</td>
<td>Juvenile spondylarthropathy</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RANKL</td>
<td>Receptor activator of nuclear factor kappaB ligand</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RF</td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td>ROB-FIN</td>
<td>Registry of Biologic Treatment in Finland</td>
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<tr>
<td>sc</td>
<td>Subcutaneous</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>sJIA</td>
<td>Systemic juvenile idiopathic arthritis</td>
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<tr>
<td>SUN</td>
<td>Standardization of Uveitis Nomenclature</td>
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<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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<tr>
<td>VAS</td>
<td>Visual analog scale</td>
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</table>
1 INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of disorders of unknown etiology and the main connective tissue disease in childhood and adolescence. JIA is a major cause of functional disability and eye disease in childhood. In Scandinavia, the approximate incidence of JIA is 15 per 100,000 children, and the prevalence 0.1%. In 40-60% of these individuals, the burden of disease is high and the consequences may be life-long. Subtypes of JIA have clinically distinct disease courses and long-term outcomes. At least juvenile polyarthritis, extended oligoarthritis, and systemic JIA (sJIA) are associated with highly active rheumatic inflammation.

A refractory course of JIA may require long-term use of glucocorticoids, which, together with chronic inflammation, are known to induce growth impairment. Glucocorticoid treatment has been suggested to induce irreversible damage to growth in one-third of JIA patients receiving steroids, and in all of those receiving steroids for more than one year, possibly due to a direct effect on growth plates and other growth-modulating pathways. However, in JIA growth has been documented to slow down also without preceding steroid treatment. Decreased final height has been shown to associate with physical disability, and decreased growth velocity with disease duration and disease flares. Pro-inflammatory cytokines have been suggested to impair bone growth, but the effect of anti-TNF agents on growth is not yet thoroughly known.

Chronic, nongranulomatous uveitis, involving the anterior part of the uvea, is known to be associated with JIA in 5-30% of patients, depending on the subtype. The risk is suggested to be highest in antinuclear antibody (ANA)-positive young females with oligoarthritis. The standard therapy for anterior uveitis is topical steroids. If inflammation remains active, early immunomodulatory treatment is recommended. Methotrexate and cyclosporine A have been suggested to be beneficial in chronic uveitis. Regardless of topical and systemic therapy, up to one-third of affected eyes may develop impaired vision and one-tenth may become blind.

Conventional therapy for JIA consists of nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), and oral or intravenous (iv) corticosteroids along with nonpharmacologic interventions, including physiotherapy and orthoses. Approximately 20-30% of all JIA patients, mostly those with a highly active polyarthritis, a systemic disease, or a vision-threatening uveitis may respond inadequately to conventional DMARDs. During the last decade biotechnology has developed new immunomodulatory molecules for treatment of these refractory patients. Among the first biologic drugs are anti-TNF agents, which have been in clinical use for JIA patients in Finland since 1999. Etanercept is a soluble TNF receptor, and infliximab a chimeric monoclonal TNFα antibody. Both have been proven effective in treating JIA in randomized controlled trials (RCTs). Since 2003, a humanized monoclonal TNFα antibody, adalimumab, effective in treating rheumatoid arthritis (RA), has been available for JIA patients. TNFα blockers are highly effective in JIA, but their action in childhood uveitis is yet not well known.

Until recently, placebo-controlled and randomized studies on drug therapy in pediatric rheumatology were almost nonexistent. At present, international collaboration has enabled
larger patient series, thus providing more reliable data on efficacy of both biologic and conventional drug therapies in JIA, but not yet in childhood uveitis. Within the limits of a reasonable recruitment phase, the sample sizes in single-center or national studies are usually too low to conduct controlled or even observational studies in different subpopulations of JIA.

Our primary focus here was on the long-term safety and efficacy of biologic agents in children. Knowing the problems in the research field of pediatric rheumatology mentioned above, all JIA patients from the largest Finnish tertiary centers in Helsinki, Heinola, and Oulu were included in this study. We reviewed patient charts of all children who had received biologic agents since 1999. To enable and facilitate future studies, and as an amendment to the Registry of Biologic Treatment in Finland (ROB-FIN), our study group founded a children’s register in 2005 with already collected data as the grounding. This national ROB-FIN registry was established in 2000 for noncommercial postmarketing surveillance of patients with RA, and is comparable to registers in e.g. Sweden, Germany, and the UK.

Our interest in growth stemmed from the fact that normal growth reflects the overall well-being of a child, and from preliminary clinical observations of growth reconstitution in JIA with use of biologic agents. We were also interested in the effect of biologic therapy on childhood uveitis, based on a preliminary clinical finding that chronic uveitis seemed to improve in a number of patients receiving anti-TNF agents. By 2003, few studies on treatment options for chronic uveitis had been published, and only controversial studies or case reports were available on biologic treatment in childhood uveitis. Finally, we wanted to get an overview of the use of different biologic agents in JIA based on our long-term follow-up.
2 REVIEW OF THE LITERATURE

2.1 Juvenile idiopathic arthritis (JIA)

2.1.1 Classification and subtypes of JIA

Chronic arthritides of childhood are a heterogeneous group of disorders of unknown etiology. Their classification has been a source of confusion over the years, with inconsistent or overlapping terminology. The term juvenile chronic arthritis (JCA) has been used in Europe and juvenile rheumatoid arthritis (JRA) in North America. JCA was proposed by the European League Against Rheumatism (EULAR) and JRA by the American College of Rheumatology (ACR). The lack of internationally accepted criteria was a major obstacle in identifying homogeneous groups of juvenile arthritis for research purposes in immunogenetics, basic science, epidemiology, outcome studies, and therapeutic trials. This need led to the formation of the Classification Taskforce of the Pediatric Standing Committee of the International League of Associations of Rheumatology (ILAR), and the term juvenile idiopathic arthritis (JIA) was introduced. ILAR proposed revised classification criteria for JIA in Durban in 1997, and a second revision in Edmonton in 2001. The majority of recent studies and virtually all international multicenter trials currently use the ILAR criteria.

JIA is not a single disease, but an entity including all forms of arthritides of childhood that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown etiology. Arthritis manifests as a joint swelling or limitation of joint motion with pain or tenderness on motion. Seven disease categories have been recognized on the basis of features present or absent (inclusion and exclusion criteria) during the first 6 months of illness (Table 1). Those fulfilling criteria in no category or in more than one category are defined as undifferentiated arthritis. Apart from classification criteria, a few descriptors are usually presented to gain further information about the outcome and the clinical features of each patient. Descriptors, such as presence of ANA, acute or chronic anterior uveitis, age at onset, and location of arthritis, are of clinical interest and may in the future enable reclassification of JIA. However, scientific evidence of the value of these descriptors in classification criteria is still insufficient.

A relationship exists between the subtypes of juvenile arthritides and rheumatic diseases of adulthood. Juvenile seropositive polyarthritis is thought to be early-onset RA, and sJIA resembles adult-onset Still’s disease. Enthesitis related arthritis (ERA), affecting the entheses and axial skeleton in addition to peripheral joints, belongs to the group of spondyloarthropathies. The term includes children with juvenile ankylosing spondylitis (who meet the criteria for adult ankylosing spondylitis) and most patients with undifferentiated spondyloarthritides. In a Mexican study of children with ERA (formerly called seronegative enthesopathy and arthropathy), progression to definite juvenile ankylosing spondylitis occurred in 75% of patients.
Table 1  JIA subtypes 1-6 with inclusion and exclusion criteria, excluding undifferentiated arthritis (no. 7), based on the second revision of ILAR criteria [27].

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oligoarthritis</td>
<td>Persistent</td>
<td>Arthritis in 1-4 joints during the 1st 6 mo</td>
<td>Psoriasis or 6c; 5b with 5c; 5e or these disorders in a patient; 3a; sJIA</td>
</tr>
<tr>
<td></td>
<td>Extended</td>
<td>1a. affects &lt; 5 joints throughout disease</td>
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<tr>
<td></td>
<td></td>
<td>1b. affects ≥ 5 joints after the 1st 6 mo</td>
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</tr>
<tr>
<td>Polyarthritis</td>
<td></td>
<td>Arthritis in ≥5 joints during the 1st 6 mo</td>
<td>Psoriasis or 6c; 5b with 5c; 5e or these disorders in a patient; sJIA</td>
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<td></td>
<td>2. Seronegative</td>
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<tr>
<td></td>
<td>3. Seropositive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Systemic arthritis</td>
<td></td>
<td>Arthritis in ≥ 1 joints with or prior to 2-week fever(^1) and ≥ 1 of following:</td>
<td>Psoriasis or 6c; 5b with 5c; 5e or these disorders in a patient; 3a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4a. Erythematous nonfixed rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4b. Generalized lymph node enlargement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4c. Hepato- and/or splenomegaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4d. Serositis(^2)</td>
<td></td>
</tr>
<tr>
<td>5. Enthesitis related arthritis</td>
<td></td>
<td>Arthritis and enthesitis(^3), or arthritis or enthesitis with ≥ 2 of following:</td>
<td>Psoriasis or 6c; 3a; sJIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5a. Present or history of SI tenderness and/or inflammatory lumbosacral pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5b. Presence of HLA-B27</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5c. Onset of arthritis in males aged &gt;6y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5d. Acute symptomatic anterior uveitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5e. History of AS, ERA, sacroiliitis with IBD, Reiter’s syndrome, or acute anterior uveitis with IBD, Reiter’s syndrome, or acute anterior uveitis in 1° degree relative</td>
<td></td>
</tr>
<tr>
<td>6. Psoriatic arthritis</td>
<td></td>
<td>Arthritis and psoriasis, or arthritis and ≥ 2 of following:</td>
<td>5b with 5c; 5e or these disorders in a patient; 3a; sJIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6a. Dactylitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6b. Nail pitting or onycholysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6c. Psoriasis in 1° degree relative</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) fever: daily and quotidian (rises to ≥ 39°C daily and returns to ≤ 37°C between fever peaks) ≥ 3 days  
\(^2\) serositis: pericarditis and/or pleuritis and/or peritonitis  
\(^3\) enthesitis: tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone  

See “Abbreviations” for further definitions. AS ankylosing spondylitis, ERA enthesitis related arthritis, IBD inflammatory bowel disease, mo months, SI sacroiliac joint, sJIA systemic JIA, y years
2.1.2 Epidemiology of JIA

JIA is the most common rheumatic disease in childhood. The exact frequency of JIA is unknown, but it has been described in all geographic areas. A comparison of published data on the occurrence of JIA is challenging due to inconsistent disease definitions, underreporting, and studies involving both individual centers and pooled data from regional populations.

In a Caucasian population of subjects less than 16 years of age, the reported prevalence of JIA from studies published during the last two decades ranges from 20 to 200 per 100,000 (Europe, USA, Canada), and in Scandinavian studies from 86 to 148 per 100,000. Based on investigations of Gäre et al. and Moe et al., the estimated prevalence in Scandinavia is approximately 1 per 1000 children. The incidence of JCA or JIA varies between 2 and 23 per 100,000, but is reported in most studies between 8 and 15 per 100,000. In the Finnish population, the reported incidence was 13.8-15.1 in 1980-1990, 18.2 in 1982-1983, 19.5 in 1995, and 21 per 100,000 in 1997-1999.

The age at disease onset depends greatly on the subtype. Especially in girls, the incidence is highest between 1 and 3 years of age. Approximately twice as many girls as boys are affected, although this proportion varies in different subtypes. Oligoarthritis is the most common subtype, comprising more than half of the cases, while approximately one-quarter of patients have polyarthritis, and in Scandinavia, less than one-tenth have sJIA. Ravelli et al. suggested ANA positivity to be considered as a modifier for diagnostic criteria. This proposal was based on a finding that ANA positive patients with similar characteristics in terms of age at onset, gender, and frequency of symmetric arthritis and uveitis now belong in several different JIA categories and subcategories. The proportion of patients in each category has been of interest in recent publications (Table 2). In a recent population-based Scandinavian study, 63% of patients were female and 34% male. Of females, 42% were ANA-positive and of males 34%. Oligoarticular disease was observed in 66%, polyarticular disease in 23%, psoriatic arthritis in 3%, and sJIA in 4%. Only 3% of patients were rheumatoid factor (RF)-positive, 4% had ERA, and 24% had unclassified arthritis.

Globally, the proportion of oligoarthritis is 27-56%, being more common in females. In persistent oligoarthritis, peak incidence occurs at 1-2 years, and ANA may be present in up to 80% of cases. Up to 50% of those with oligoarticular onset may eventually develop into extended disease. Polyarthritis occurs in about 30% of patients, with a female predominance, and onset of disease is observed throughout childhood, with a peak at 1-3 years. RF is present in less than 5% of subjects, and is more common in adolescent girls. Systemic arthritis affects both sexes equally; onset is seen throughout childhood, and occurs in 4-17% of JIA patients. Of JIA patients, 3-16% belong to a category of ERA in which also those with juvenile spondylarthropathy (JSPA) are classified. ERA is strongly associated with the presence of human leukocyte antigen B27 (HLA B27). Approximately 2-11% of patients belong to the category of juvenile psoriatic arthritis (PsA).
### Table 2 Proportion (%) of patients in each category and subcategory of JIA in recent publications with an epidemiologic focus and mainly population-based data.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>(n)</th>
<th>Oligoarthritis</th>
<th>Polyarthritis</th>
<th>sJIA</th>
<th>ERA</th>
<th>PsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minden 2002</td>
<td>(215)</td>
<td>40</td>
<td>13</td>
<td>1</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Thomson 2002</td>
<td>(421)</td>
<td>30</td>
<td>15</td>
<td>20</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Berntson 2003</td>
<td>(315)</td>
<td>41</td>
<td>5</td>
<td>19</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Merino 2005</td>
<td>(125)</td>
<td>43</td>
<td>20</td>
<td>2</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Pruunsild 2007</td>
<td>(160)</td>
<td>44</td>
<td>11</td>
<td>21</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

See “Abbreviations” for further definitions. PsA psoriatic arthritis

1 Hospital-based study, regional population (long-term outcome; disease onset in 1978-1988) in Berlin
2 JIA cohort of Caucasian origin in multicenter study (17 centers) for HLA associations in the UK
3 Multicenter study, regional population from Scandinavia (1997-1998), 24% had unclassified arthritis
4 Hospital-based study, regional cohort in Madrid
5 Hospital- and population based study in Estonia (1999-2001)

### 2.1.3 Long-term outcome of JIA

In the evaluation of outcome, the focus has traditionally been on physical and functional measures, i.e. disease activity, joint damage, and physical disability. Steinbrocker classes are adult-oriented and rough, but have been used as a measure of functional status in patients with JIA for almost 6 decades. The classes range from I (complete functional capacity with ability to carry on usual duties without handicaps) to IV (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care). A self-administered Health Assessment Questionnaire (HAQ) has been validated to evaluate the physical function in RA, and a self- or parent-administered Childhood HAQ (CHAQ) is a comparable measure for juvenile patients. Both the currently used HAQ and CHAQ cover 8 activity areas; dressing and grooming, rising, eating, walking, hygiene, reaching, gripping, and other activities; providing an overall disability score within range 0-3. Compared to HAQ, in CHAQ for each functional area several questions has been added, including at least 1 question relevant to children of all ages. In long-term outcome studies the evaluation with CHAQ is increasing, although not wide yet. Other measures assessing long-term damage in JIA are available but rarely used, such as modified Sharp/van der Hejde Score or Poznanski score, in which the radiographic damage is assessed either by carpo-metacarpal ratio or by carpal length, respectively. A clinical measure for articular and extraarticular damage, a Juvenile Arthritis Damage Index (JADI), has been published in 2005 and is currently in experimental use. Outcome domains for JIA can also include psychosocial well-being, pain perception, socioeconomic status, osteoporosis, growth, surgical procedures, and ocular sequelae.
In the past, 80% of children have been suggested to reach adulthood in clinical remission. This optimistic view has been challenged by a number of recent studies. The proportion of JIA patients achieving remission was 40-60% during a follow-up period of up to 28 years. Approximately 10% of these patients had severe functional impairment, measured by Steinbrockers’ functional class III or IV.

Subtype-specific outcome

The outcome seems to be associated with the subtype of JIA, being the best in persistent oligoarthritis and worst in RF-positive polyarthritis. However, in persistent oligoarthritis, chronic uveitis or unremitting arthritis causes increased morbidity. In extended oligoarthritis, the morbidity resembles that of polyarthritis, or is even worse (Table 3). Systemic symptoms in sJIA are often self-limited, but in up to half of patients the disease may be long-lasting and arthritis destructive. Foster et al. observed that more patients with polyarthritis, sJIA, or psoriatic arthritis had physical disabilities than patients in other JIA categories. Bowyer et al. documented that after 5 years from disease onset more than 25% of patients with polyarthritis and nearly a half with sJIA had functional limitations, and altogether two-thirds had radiographically evident joint space damage.

In a Norwegian study, half of the 133 JRA patients were in remission after a median of 15 years from disease onset. The remission rate was 35% in extended oligoarthritis, 15% in seropositive polyarthritis, 46% in seronegative polyarthritis, and 76% in sJIA. In long-term follow-up studies, the proportion of patients in clinical remission has been 33-80% in sJIA, 0-25% in seropositive polyarthritis, 23-46% in seronegative polyarthritis, 7-35% in extended oligoarthritis, and 42-73% in persistent oligoarthritis. The remission rate has been demonstrated to increase during the first 5 years from disease onset, reach its peak at years 5-10 and then slowly decline. Altogether 91% of remissions occur before the 16th birthday. Recently, the time spent in active and inactive disease was evaluated. The majority of patients with extended oligoarthritis, polyarthritis, and sJIA spent nearly two-thirds of their time with active disease. Although 44% achieved clinical remission off medication, it lasted less than 2 years in the majority and 5 years in only 6% of patients.

A review of the results in a regional cohort with JIA onset 2-3 decades ago in Berlin provides a good insight into the possible long-term physical consequences of JIA. In 1998-1999, half of the patients still had active disease and/or long-term complications of rheumatic disease. At a 17-year follow-up, the physical status and complications of the cohort were as follows: limitation of motion in more than 4 affected joints in 12-100% depending on subtype, leg length disturbances in 25%, uveitis and/or visual impairment in 14%, micrognathia in 10%, cardiac involvement due to rheumatic disease in 5%, hip or knee prostheses in 2% (8 prostheses in 5 patients), amyloidosis with renal insufficiency in 1%, and growth retardation (unspecified). In addition, 45% had undergone surgery due to complications of JIA.
Table 3  Subtype-specific long-term outcome and disease activity in severe JIA. The proportion of patients in JIA categories is presented, when available.

<table>
<thead>
<tr>
<th>Author and year (n)</th>
<th>Disease duration (years)</th>
<th>Subtypes (% of each study cohort)</th>
<th>Active disease (%)</th>
<th>Steibrocker's class III-IV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Poly RF+/-</td>
<td>Ext-oligo</td>
<td>sJIA</td>
</tr>
<tr>
<td>David 1994 (43)</td>
<td>20</td>
<td>30 / 21</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Zak 2000 (65)</td>
<td>26</td>
<td>26</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Lomater 2000 (80)</td>
<td>11</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>Fantini 2002 (530)</td>
<td>11</td>
<td>4 / 12</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Minden 2002 (215)</td>
<td>17</td>
<td>1 / 13</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Oen 2002 (392)</td>
<td>11</td>
<td>10 / 20</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Packham 2002 (246)</td>
<td>28</td>
<td>15 / 17</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Flatø 2003 (268)</td>
<td>15</td>
<td>13 / 23</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Foster 2003 (82)</td>
<td>21</td>
<td>15 / 24</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Arkela-K 2005 (123)</td>
<td>16</td>
<td>3 / 19</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Flatø 2006 (55)</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

P RF+/- or poly RF+/- seropositive/seronegative polyarthritis, Ext-oligo or Eo extended oligoarthritis, S or sJIA systemic arthritis, E or ERA enthesitis related arthritis, - no data

Mean or median, ²In earlier studies juvenile SPA, ³Severe disability in those with P/Eo/S/E (OR whole cohort)

A limited number of studies describe the outcome in ERA. In a recent case-control study,²⁹ patients with ERA had poorer physical health and more bodily pain than those with oligoarthritis or polyarthritis or controls in the general population. Among ERA patients with a median disease duration of 23 years, sacroiliitis was observed in 35% and reduced spinal flexion in 75%.²⁹ Persistent disease is reported to most often be seen in patients with polyarthritis and extended oligoarthritis⁵⁰ or ERA.²⁹

Early predictors of unfavorable outcome

A number of predictive factors have been suggested for poor outcome, measured by physical disability, radiographic damage, and/or unremitting disease. These include articular severity score;⁷¹ prolonged active disease, late admission, and late start of DMARDs;⁶⁵ female gender and positive RF;⁶¹,⁶⁴ HLA-B27 present and onset age of more than 6 years;⁷² HLA-B27;⁶¹,⁷³ HLA-B27, DRB1*01, DRB1*08, polyarticular disease, symmetrical arthritis, young age at onset, hip involvement, and long duration of elevated erythrocyte sedimentation rate (ESR);⁶¹ young age at onset and greater restricted joint count.⁷⁴ For sJIA, male gender⁷⁵ and persistent systemic features with thrombocytopenia at 6 months from onset are predictors for physical disability.⁷⁶ The latter is suggested to also be a predictor of articular damage,⁷⁷,⁷⁸ as is also the presence of pulmonary or cardiac serositis within 6 months from onset.⁷⁹ However, at diagnosis none of these measures can accurately predict which children will have unfavorable outcome and require the most aggressive treatment.
**Disturbances in growth and pubertal development**

One of the permanent complications of JIA is growth impairment and reduced final height, which is seen especially in polyarthritis and sJIA. Physical disability may be associated with decreased final height. Both active inflammation and concomitant intake of glucocorticoids can cause a reduction in linear growth. Growth has been reported, however, to slow down also without previous steroid treatment. Immobilization, direct damage to the joints involved, and poor nutrition have also an impact on growth.

Normal growth requires the presence of normal thyroid function, and the pulsatile secretion of growth hormone (GH) with GH-dependant insulin-like growth factor-1 (IGF-1). Both normal and impaired spontaneous or stimulated GH secretion has been reported in children with JIA and severe growth retardation. It has been suggested that the underlying mechanism of growth impairment in JIA is not classical GH deficiency, but GH insensitivity.

Improvement of growth rate and even achievement of target height have been documented in several patients receiving GH, but the results in different series are inconsistent, and growth is not restored in all patients. In a recent RCT, significantly more of the 13 patients treated with GH were reported to reach expected final height than the 18 subjects in the control group. A significant difference in height outcome existed, however, only in patients with moderate disease activity, but not in those with high disease activity.

In a retrospective study of 37 patients with polyarthritis or sJIA, significant negative relations were found between disease duration and growth velocity, and disease flares and growth velocity. Of those whose growth decreased ≥ 1 height Z-scores, none entering remission had catch-up growth. In another study of 22 sJIA patients, 30% had no catch-up growth after prednisolone discontinuation. In all 22, the mean final height was -2.0 ± 1.8 height standard deviation scores (HSDS), which was below target height in 87%. Wang et al. suggested that irreversible growth impairment occurs, once the glucocorticoid treatment has lasted for more than a year.

It is commonly assumed that a chronic disease in childhood delays puberty. Delayed bone age can reflect a delayed maturation process also in prepubertal children. Studies concerning onset of puberty or skeletal maturation in JIA are few. In the timing of menarche, a significant difference was observed between 68 JRA patients and 46 controls. Menarche was delayed most in those with polyarthritis. Duration of disease was a weak predictor for the timing of menarche. In an Italian study, 83 JCA patients with or without glucocorticoid treatment, all but especially those on steroids had delayed timing of menarche compared with their mothers and healthy girls. In contrast, a Swedish study on reproduction ability of young adults reported that menarche occurred at a median age of 13 years both in 126 females with JCA and in 117 healthy controls.

Local inflammation and production of growth factors may cause overgrowth of the affected limb or a premature fusion of the involved epiphyses, resulting in diminished length. Arthritis in the lower limb may thus result in discrepancy of leg lengths. Micrognathia and retrognathia are examples of localized growth disturbances in temporomandibular joints. Arthritis in wrists or elbows may advance bone age.
A failure to develop adequate bone mineralization has been common in children with JIA and is characterized by impaired bone formation and a failure to undergo a normal increase in bone mass during puberty. Thus, the potential of JIA patients to achieve an adequate peak skeletal mass may be markedly decreased. The onset of accelerated skeletal maturation with puberty is a critical period of potential intervention in JIA. Therapeutic interventions later during adolescence are less promising in reversing inadequate bone mineralization. In a recent Finnish study on bone health in a JIA cohort of 62 patients, bone age was delayed by ≥ 1 year in 24% and advanced by ≥ 1 year in 19%. Areal bone mineral density (aBMD) Z-scores for the lumbar spine were only slightly below the population mean, and the occurrence of asymptomatic vertebral fractures was 10%. The frequency of osteopenia in this cohort was markedly lower than in patient series with disease onset before the wider use of immunosuppressive and biologic agents, reflecting the improved treatment regimens.

### 2.1.4 Assessment of disease activity and treatment response

In adult RA, ACR criteria has been produced to measure treatment response, ACR20, ACR50, and ACR70 showing 20%, 50% and 70% improvement in core sets of criteria, respectively. To achieve ACR20, improvement of ≥ 20% in both swollen and tender joint counts is required, as well as ≥ 20% improvement in 3 of following 5: patient pain assessment, patient global assessment, physician global assessment, patient self-assessed disability (e.g. HAQ), and acute phase reactant (ESR or CRP). Additionally, EULAR has produced a measure for disease activity, a Disease Activity Score (DAS), which was further modified to the DAS in 28 joints (DAS28). One of a few comparable equations in calculating DAS28, where TEN28 is equal to 28-joint count for tender joints, SW28 for swollen joints, and GeH to general health assessed by visual analog scale (VAS), is as follows:

\[
\text{DAS28} = 0.56 \times \sqrt{TEN28} + 0.28 \times \sqrt{SW28} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GeH}
\]

Substantial differences exist between ACR criteria and DAS; the former were developed to distinguish differences between active treatment and placebo, and the latter between high and low disease activity. ACR criteria define improvement on the basis of relative variation, whereas DAS includes absolute variation and the level achieved. ACR criteria include two outcome categories (responder/ nonresponder), and DAS three (good, moderate, absent). In clinical trials, ACR criteria and DAS perform similarly in identifying responders. Juvenile DAS, JADAS, is currently being developed and validated.

**American College of Rheumatology (ACR) Pediatric criteria**

In 1997, Giannini et al. defined preliminary core sets of criteria and a definition of improvement in JIA, termed as the ACR pediatric 30% response criteria (ACR Pedi30).
This definition is comparable with the ACR criteria in adult RA, but no measure comparable with DAS has yet been validated for children.

ACR Pedi30 includes improvement of at least 30% from baseline in 3/6 core set variables, whereas in ACR Pedi50 the improvement must be at least 50%, and in ACR Pedi70 at least 70%. The 6 core set variables are as follows: number of active joints, number of joints with limitation of motion and pain or tenderness, physician’s assessment of disease activity, parent’s assessment of the well-being of the child, a validated measure of physical function, and a laboratory measure of inflammation. Most often, physicians and parents use a 100-mm VAS to measure disease activity and child’s well-being, respectively. Physical function is evaluated by CHAQ, and the level of inflammation by ESR or C-reactive protein (CRP). To fulfill the definition of improvement, no more than 1 of the remaining variables can worsen by more than 30%. A recent study reported a low correlation between the tender joint count and CHAQ early in the disease course, but a high correlation in longstanding disease. A minimum of 40% worsening in a minimum of 2/6 core set variables, with no more than 1 variable improving by ≥ 30%, has been suggested as a preliminary definition of disease flare.

ACR Pediatric measures primarily the relative efficacy in the context of clinical trials and is less useful in quantifying or assessing longitudinal response or describing disease activity at a specific moment. The relation between the ACR and EULAR criteria in JIA has recently been examined in a cohort of 75 children with polyarticular JIA receiving methotrexate (MTX) or TNFβ inhibitors. The highest concordance was observed between the DAS and the ACR Pedi30, the lowest between the DAS28 and the ACR20. The researchers suggested that the ACR Pedi30 could be used in adult patients affected with JIA, and that the original DAS was an alternative to the ACR Pedi30 in children and adolescents with JIA. Future studies will determine whether DAS is responsive enough to be used as continuous measure of disease activity in children.

The outcome measures mentioned above do not include any specific criteria for evaluating the potential activity of uveitis, instead focusing on arthritis.

**Inactive disease and remission**

The primary goal of the management of JIA is the achievement and maintenance of remission, defined as the absence of all active rheumatic disease, i.e. arthritis and systemic features, including uveitis. The preliminary criteria of inactive disease for JIA is defined as follows: no active synovitis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR and/or CRP; and physician’s VAS indicating no active disease. No consensus has been reached in the definition of inactive uveitis, in which the required anterior chamber cell activity ranges from grade 0 to 1+. **Clinical remission on medication** is defined as 6 continuous months of inactive disease on medication. **Clinical remission off medication** is defined as 12 continuous months of inactive disease off all anti-arthritis and anti-uveitis medications. These definitions provide a first important step towards standardization of reporting of remission rates,
which can also be useful as the outcome measures of therapeutic trials. However, they have not been prospectively validated. An interesting investigation of adult RA reported that 96% of patients, classified as being in clinical remission based on clinical examination by consultant rheumatologists, had evidence of synovitis in gadolinium-enhanced magnetic resonance imaging (MRI).105

2.2 JIA-associated uveitis

2.2.1 Inflammation of the uvea

Uveitis is an inflammation of the uveal tract of the eye, composed of the iris, ciliary body, and choroid (Figure 1). As early as in 1987, the International Uveitis Study Group (IUSG) recommended the subdivision of uveitis by affected structure.106 In 2005, the international consensus workshop of the Standardization of Uveitis Nomenclature (SUN) endorsed and completed this classification.

Anterior uveitis (including iritis, iridocyclitis, and anterior cyclitis) refers to an inflammation of the anterior chamber (AC). Intermediate uveitis (including pars planitis, posterior cyclitis, and hyalitis) involves the vitreous, and posterior uveitis (including focal, multifocal, or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis, and neuroretinitis) the retina or choroid. The term panuveitis describes a uveitis that involves the AC, vitreous, and the retina or choroid. The primary site of inflammation is determined clinically.106, 107

The onset of uveitis can be described as sudden or insidious. The duration can be either limited (≤ 3 months) or persistent. The course can be chronic (persistent uveitis with relapse in less than 3 months after discontinuing treatment), recurrent (repeated episodes separated by periods of inactivity without treatment ≥ 3 months in duration), or acute (sudden onset and limited duration).107

The inflammation is marked by leukocytic infiltration and an increase in vascular permeability, which an ophthalmologist can visualize directly using a slit lamp.108 In the normally clear media of the AC and vitreous cavity, during inflammation leukocytes can be identified and quantified, and the extravasated protein in the anterior eye is visible as a haze, referred to as “aqueous flare”. The anatomic location of uveitis determines the clinical features. In anterior uveitis, photophobia, tearing, redness around the iris, and blurred vision are common. The ophthalmologic examination may reveal ciliary injection (congestion of vessels at the corneoscleral junction), keratic precipitates (collections of leukocytes on the internal surface of the cornea), aqueous cells and flare, anterior synechiae (iridocorneal adhesions), posterior synechiae, and/or iris nodules.108 Anterior JIA-associated uveitis has an unusual presentation, most often being asymptomatic. It is therefore detected by routine screening only.
2.2.2 Epidemiology of JIA-associated uveitis

A systemic inflammatory disease, most commonly an HLA-B27 associated spondylarthropathy, sarcoidosis, and, in children, JIA, is associated with uveitis in half of all patients referred to tertiary care facilities. Population-based studies in Caucasian patients have suggested that the overall annual incidence of uveitis is 11-23 per 100,000, and the estimated prevalence is 75-200 per 100,000. The prevalence seems to be higher in the developing world, where the infectious causes of uveitis, e.g. tuberculosis and toxoplasmosis, are more frequent, and asymptomatic uveitis is virtually never screened. Compared with adults, uveitis is considerably less common in children, being observed in approximately 5% of all uveitis cases.

Due to the rarity of childhood uveitis, population-based surveys are few, and with small patient series of limited value. In a recent Finnish study, the incidence and prevalence per 100,000 for anterior uveitis was 4.0 and 25, and for JIA-associated uveitis 1.1 and 13.9, respectively. Of the 55 patients with childhood uveitis, 91% had anterior and 82% JIA-associated or idiopathic uveitis. Of note, the term idiopathic uveitis is presumed to
represent a local autoimmune process of the eye. In a British study, the incidence of uveitis in patients less than 16 years was 4.9 per 100,000. In the whole cohort of 249 patients aged under 20 years at onset, 54% had chronic anterior, 16% acute anterior, and 30% posterior uveitis, the etiology of the latter being toxoplasmosis or idiopathic. In this cohort, uveitis was idiopathic in 44% of patients and JIA-associated in 47%.

Noninfectious uveitis is associated with JIA in approximately 20% of patients. In most cases, uveitis is asymptomatic anterior chronic iritis or iridocyclitis with bilateral involvement. In one-tenth of patients, uveitis is detected before arthritis. However, in a long-term follow-up, Guillaume et al. found no higher risk for uveitis in those with than without ANA, or in those with extended vs. persistent oligoarthritis.

In patients with oligoarthritis, uveitis is observed in 16-47%, and the risk has been reported to be higher in persistent or extended disease, compared with other subtypes. Uveitis occurs in 5-24% of patients with seronegative polyarthritis and in 2-23% of those with PsA, but is uncommon in patients with seropositive polyarthritis and sJIA. Uveitis may also be acute, with a much better prognosis, especially with HLA-B27 or ERA-associated disease, in which 8-28% of the patients are affected. Patients with remission in arthritis may have a highly active uveitis, and most often uveitis and arthritis seem to follow different courses, although some controversy exists.

2.2.3 Complications and visual outcome

Unless uveitis is detected and treated early, patients are at risk of developing severe visual impairment, visual loss, and other sequelae. In 1988, in a study of 315 JCA patients with uveitis, approximately one-fourth were reported to have an excellent visual prognosis, one-half a more severe, but still controllable uveitis with topical medication, and one-fourth a poor visual prognosis. During the last decade, the use of systemic medication has become more frequent in patients with uveitis. In 2007, one-half were reported to require immunosuppressives. Even though a decreased incidence of complications has been observed, the rate in the latest publications is still high; 49-71%. Complications include cataract in 22-71%, glaucoma in 15-32%, band keratopathy in 14-66%, posterior synechiae in 22-28%, macular edema in 3-6%, and ocular hypotony in 4-19% of patients. The highest complication rates have been reported in those with seronegative polyarthritis (67%) or extended (58%) or persistent (54%) oligoarthritis.

Abnormal vision is associated with synechiae or cataract, and worse visual prognosis with longer delay before referral to a specialist.

The visual outcome is usually reported as the best-corrected visual acuity (BCVA). Visual loss is defined as BCVA ≤ 0.1 (equals to ≤ 20/200), visual impairment as BCVA 0.2-0.4 (equals to 20/100 - 20/50), and good visual acuity as ≥ 0.5 (equals to ≥ 20/40). The reported rate of visual loss has decreased during the last two decades, but is still considerably high. Impaired vision in 30-46% of patients in at least one eye and visual loss
Short-term reports have been published in Canada and Finland, where visual impairment occurred in 4% and 3%, visual loss in 9% and 0% of JIA patients, and an overall complication rate of 37% and 24%, respectively. The low rate may be due to better screening, earlier and more effective treatment, and/or selection bias.

Long-term outcome studies evaluating the chronicity of JIA-associated uveitis are few. In such studies with a follow-up of more than a decade, one observation is the development of uveitis in 30% of those aged over 16 years. Moreover, chronic inflammation of the eye was active in 42% and 63% after a mean duration of 16 and 21 years, respectively. At the 16- and 21-year follow-ups, ocular complications have been observed in 80% and 100% of patients, respectively. BCVA was impaired in 40% of the eyes, poor (20/150) in 20% and lost (no light perception) in 10%. Severe uveitis at initial ocular examination has been shown to correlate with worse prognosis, and systemic steroids with cataract formation.

2.2.4 Assessment of activity of uveitis

Activity of AC inflammation of uveitis is based on the quantity of cells in the AC on standard slit-lamp examination. AC inflammation is graded from 0 to 4 (grade /AC cells in field): 0 /<1, 0.5+ /1-5, 1+ /6-15, 2+ /16-25, 3+ /26-50, 4+ />50. An improved activity of uveitis is defined as either a 2-step decrease in the level of inflammation or a decrease to inactive level (grade 0), and a worsening of inflammation as either a 2-step increase in the level of inflammation or an increase to the maximum grade 4+. In healthy individuals, a rare cell (but < 1 cell per field), has been demonstrated. Inactive anterior uveitis is defined as rare or no cells, and the presence of 1 cell in every field is indicative of grade +0.5 (“trace cells”) and should not be considered inactive uveitis. Remission is defined as inactive disease for ≥ 3 months after discontinuing all treatments for eye disease.

The presence or absence of hypopyon is recorded separately. The presence of vitreous cells is an important clinical feature, but no consensus has thus far been reached on a grading system. Macular edema is reported as present or absent, as determined clinically. The term glaucoma is not considered synonymous with elevated intraocular pressure, but should be reserved for situations where either glaucomatous disk damage is observed or visual field loss is demonstrated. The term elevated intraocular pressure is used when an intraocular pressure above a defined normal range or an increase from baseline (in longitudinal data) is observed. Clinical treatment studies may evaluate either the response of active uveitis to a drug or the ability of a drug to maintain inactive disease while other drugs are tapered. Other outcome measures (e.g. discontinuation of prednisolone) can also be reported. In studies of adult patients, reduction of daily prednisolone to ≤ 10 mg while maintaining inactive uveitis can be considered as the primary outcome for successful corticosteroid sparing. In children, however, no consensus on such prednisolone doses exists.
2.3 Conventional treatment in JIA and associated uveitis

The aim in the treatment of JIA and associated uveitis is prevention of damage to joints and eyes, promotion of normal growth and development, resolution of synovitis and uveitis, and increasingly, disease remission rather than improvement. Outcome studies demonstrate that our treatments in the past have not been as effective as we would have liked. Pharmacological therapy of JIA should consider both arthritis and uveitis, as they often run independent courses. In an ideal model of treatment, patients are followed by both a pediatric rheumatologist and an ophthalmologist. A treatment program should be family-centered, and the multidisciplinary team should also include a physical and occupational therapist, a social worker, a psychiatrist, and a dentist.

The current approach to pharmacological treatment of JIA is an initial evaluation of severity of disease, followed by early treatment and close monitoring of treatment effect during the disease course. The treatment plan needs to be individualized based on JIA subtype. For patients with mild disease, such as oligoarthritis without uveitis, there is a choice of using intra-articular steroids or nonsteroidal anti-inflammatory drugs (NSAIDs), or both. If functional limitations occur, symptoms persist or worsen, or at initial visit the patient has already a polyarticular disease, more aggressive therapy should be initiated. DMARDs are most often started with MTX monotherapy. In systemic onset JIA, the initial therapy is corticosteroids. MTX may work in sJIA-related arthritis, but is usually not helpful with systemic features.18, 47

2.3.1 NSAIDs and corticosteroids

The initial symptomatic first-line therapies in JIA are NSAIDs and intra-articular steroids. NSAIDs are used in appropriate daily dose, most commonly naxopren 10-20 mg/kg, ibuprofen 20-40 mg/kg, or diclofenac 3-5 mg/kg,128, 129 and are combined frequently with DMARDs and/or glucocorticoids. NSAIDs provide analgesic and mild anti-inflammatory benefits by inhibiting the cyclooxygenase-2 isoenzyme in the prostaglandin biosynthetic pathway. Traditional NSAIDs concomitantly inhibit the cyclooxygenase-1 isoenzyme, but are associated with gastrointestinal toxicity. Cyclooxygenase-2 selective inhibitors have been associated with less gastrointestinal symptoms and have become a treatment option in RA. In a double-blind RCT, the efficacy of meloxicam, which is semi-selective, and rofecoxib in JIA was comparable with that of naproxen.130, 131 Due to emerging toxicity, such as adverse cardiovascular events in adults, rofecoxib was later withdrawn from the market worldwide, as were some other cyclooxygenase-2 inhibitors.

Intra-articular steroids are an established treatment for arthritis,132, 133 especially for the oligoarticular subtype. The long-term efficacy of triamcinolone hexacetonide over methylprednisolone has been proven, particularly in knee arthritis.134 Intra-articular therapy is complemented with DMARDs and oral/iv corticosteroids when articular or systemic symptoms are uncontrolled, persistent, or life-threatening. Due to side-effects, especially those affecting bone and growth, the long-term systemic use of steroids is avoided in children. Oral glucocorticoids are usually given as low-dose and alternate-day prednisolone
(0.1-0.2 mg/kg), the initial dose with severe systemic symptoms being higher (up to 1-2 mg/kg daily). In severe disease, corticosteroids can also be given as pulse therapy (iv methylprednisolone). There is no evidence that systemic glucocorticoids are disease-modifying. Steroids have both anti-inflammatory and immunosuppressive effects, which are mediated by the inhibition of specific functions of leukocytes, such as the action of various lymphokines.46

Prolonged intake of steroids may be associated with iatrogenic Cushing’s syndrome, fractures, osteoporosis, cataract, immunosuppression, and growth retardation,6, 7, 46 especially during long-term treatment.135, 136 Glucocorticoids disturb longitudinal growth, possibly by a direct effect on the receptors of the growth plate137 and/or by interfering with other growth-modulating pathways such as the IGF-1 axis.138 In addition, a transient suppression of the pituitary-adrenal axis after intra-articular steroid injections has been described139 and is suggested to be dose-dependent.140

### 2.3.2 DMARDs and other disease-modifying drugs

The increased and earlier use of immunosuppressive drugs has improved the prognosis of JIA.5 Apart from single-center and national multicenter trials, during the last decade also international complementary networks, such as the Pediatric Rheumatology International Trials Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG), have facilitated and conducted large multinational drug trials, and provided valuable information on disease management. Unsolved issues concerning treatment of JIA still exist. For example, we do not yet know whether treatment should be initiated with single or combination DMARDs. Patients and their families may adhere better to for a monotherapy. However, with a combination the efficacy may be maintained better due to synergy. The superior efficacy of combination DMARDs over monotherapy has been demonstrated in RA,141 but no comparable studies in JIA have yet been published. Exact molecular mechanism of action of most DMARDs in rheumatic diseases is not known.

**Methotrexate** (MTX) is the initial second-line agent due to its efficacy and acceptable toxicity. After a few noncontrolled studies (Table 4),142-146 a USA/USSR collaborative placebo-controlled blinded RCT proved the efficacy of MTX in JIA.147 Another gigantic multicenter RCT, including 20 countries, was published recently. Low, intermediate, and high doses of MTX were evaluated in 595 JIA patients. Results suggest that MTX should be started with a weekly dose of 15 mg/m², and continued for at least 9-12 months before declaring a treatment failure. Initial parenteral dosing has been recommended due to variations in the absorption of higher oral doses.20 Other publications on MTX have been mostly open-label studies of short-148-151 or long-term efficacy,152 or route of administration.19, 153

Although MTX monotherapy seems to be clinically effective in approximately two-thirds of patients, radiologic progression of rheumatic disease has been reported in 67-74% of patients regardless of clinical outcome and in 80-100% of nonresponders.149, 154 Ravelli et al.151 found that patients with extended oligoarthritis responded more often to MTX than sJIA or polyarthritis patients. The superior response of extended oligoarthritis compared
with sJIA was confirmed by Woo et al.\textsuperscript{155} in a placebo-controlled blinded RCT. Based on modified ACR Pedi30, this trial failed to demonstrate significant improvement in 44 sJIA patients, even though certain outcome measures were improved.\textsuperscript{155} Based on these two well-conducted studies, MTX does not seem to be effective in sJIA.\textsuperscript{151, 155}

MTX induced no serious AEs in any of the studies reviewed in Table 4. The most common AEs are nausea, vomiting, mouth sores, loss of appetite, hair loss and malaise.\textsuperscript{20} One concern with MTX has been potential hepatotoxicity. In all patients receiving MTX, regular liver enzyme screening is recommended. Even in patients receiving high-dose MTX and multiple DMARDs, the minor abnormalities observed in liver biopsies have been reversible, and no signs of fibrosis or cirrhosis have been found.\textsuperscript{156} In a noncontrolled study, folinic acid supplementation concomitantly with MTX reduced episodes of liver transaminase elevation and gastrointestinal toxicity,\textsuperscript{157} and is thus recommended.

### Table 4

**Efficacy of methotrexate in juvenile idiopathic arthritis.**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>FU</th>
<th>Method</th>
<th>Responder rate / Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truckenbrodt (1986)\textsuperscript{19}</td>
<td>11</td>
<td>11 mo</td>
<td>retrospective</td>
<td>63% (mostly sJIA), steroid-sparing effect in 53%</td>
</tr>
<tr>
<td>Speckmeier (1989)</td>
<td>12</td>
<td>6 mo</td>
<td>open label</td>
<td>33% (sJIA), on 9 mg/m\textsuperscript{2}</td>
</tr>
<tr>
<td>Wallace (1989)</td>
<td>23</td>
<td>1.6 y</td>
<td>open label</td>
<td>91%, improvement associated with dose $\geq$ 0.3 mg/kg</td>
</tr>
<tr>
<td>Rose (1990)</td>
<td>29</td>
<td>1.5 y</td>
<td>open label</td>
<td>83% systemic, 48/46% joints w limited motion/swelling</td>
</tr>
<tr>
<td>Halle (1991)</td>
<td>30</td>
<td>1.5 y</td>
<td>open label</td>
<td>46% (all responders ANA+) in active joints</td>
</tr>
<tr>
<td>Giannini (1992)</td>
<td>127</td>
<td>6 mo</td>
<td>PC DB RCT</td>
<td>65% on 10 mg/m\textsuperscript{2}</td>
</tr>
<tr>
<td>Ravelli (1995)</td>
<td>29</td>
<td>6 mo</td>
<td>open label</td>
<td>52% reduction of active joints</td>
</tr>
<tr>
<td>Reiff (1995)</td>
<td>21</td>
<td>15 mo</td>
<td>open label</td>
<td>33% on mean 27 mg (25 mg/m\textsuperscript{2}) po/ im</td>
</tr>
<tr>
<td>Huang (1996)</td>
<td>26</td>
<td>3 y</td>
<td>retrospective</td>
<td>73% (CR or 25% reduction of active joints)</td>
</tr>
<tr>
<td>Ruperto (1998)</td>
<td>111</td>
<td>6 mo</td>
<td>open label</td>
<td>66% (preliminary ACR Ped30)</td>
</tr>
<tr>
<td>Ravelli (1998)</td>
<td>257</td>
<td>6 mo</td>
<td>open label</td>
<td>58% vs. 61%, po vs. sc 10 mg/m\textsuperscript{2}</td>
</tr>
<tr>
<td>Ravelli (1999)</td>
<td>80</td>
<td>6 mo</td>
<td>open label</td>
<td>65%, CR in 36% at median of 11 mo</td>
</tr>
<tr>
<td>Woo (2000)</td>
<td>88</td>
<td>4+4mo</td>
<td>PC DB RCT</td>
<td>48% in Eo, 25% sJIA (modified ACR Ped30)</td>
</tr>
<tr>
<td>Alsufyani (2004)</td>
<td>61</td>
<td>&gt;3 mo</td>
<td>retrospective</td>
<td>66%. Nonresponders to sc-injections, and 76% improved</td>
</tr>
<tr>
<td>Ruperto (2004)</td>
<td>595</td>
<td>6 mo</td>
<td>RCT</td>
<td>72% ACR Ped30, 61% Ped50, 38% Ped70, CR 12% (No PsA, ERA) 10 mg/m\textsuperscript{2} po/sc</td>
</tr>
<tr>
<td>Ruperto (2004)</td>
<td>80</td>
<td>12 mo</td>
<td>RCT</td>
<td>15 mg/m\textsuperscript{2}: ACR 30-50-70-CR &gt; 63-58-45-13%</td>
</tr>
<tr>
<td>(non-responders) (Phase II)</td>
<td></td>
<td></td>
<td></td>
<td>30 mg/m\textsuperscript{2}: &gt;58-55-48-10% (difference p=ns)</td>
</tr>
</tbody>
</table>

See “Abbreviations” for further definitions. CR clinical remission, DB double-blind, Eo extended oligoarthritis, FU follow-up (mean/median), mo months, PC placebo-controlled, y years

Several DMARDs have been used or are still in use for JIA patients. The efficacy of hydroxychloroquine or aurothiomalate (gold sodium thiomalate) has not been proven in children. In a RCT on 72 JRA patients, comparable improvement was observed in those receiving hydroxychloroquine, aurothiomalate, and D-penicillamine. Hydroxychloroquine was better tolerated than the other drugs. However, in a USA/USSR collaborative trial, 162
JRA patients were randomized in a blinded fashion to receive hydroxychloroquine 6 mg/kg daily, D-penicillamine, or placebo. At the end of the trial, no differences were found between either hydroxychloroquine, penicillamine, or placebo. Another blinded placebo-controlled USA/USSR collaborative RCT, conducted in 231 children, showed no significant clinical efficacy with auranofin (oral gold compound) compared with placebo, even though auranofin was well-tolerated. A 5-year open-label extension trial on auranofin also revealed no sufficient therapeutic effect. No placebo-controlled studies exist on the parenteral gold compound aurothiomalate in children.

The efficacy of sulfasalazine over placebo in juvenile polyarthritis and oligoarthritis has been demonstrated in a 24-week blinded placebo-controlled RCT. Of 69 patients, 75% completed the trial. One-third withdrew from the sulfasalazine group mainly due to AEs. The most common AEs were gastrointestinal symptoms, which occurred more often in the sulfasalazine than in the placebo group, and were in one patient defined as severe. Long-term efficacy of early active sulfasalazine treatment has been evaluated in an extension study, where the original cohort was followed for a median of 9 years. At follow-up, 15% were in clinical remission off medication, 11% were in clinical remission on medication, and 74% had active disease. Those in the initial sulfasalazine group more frequently had quiescent disease and were more often ACR Pedi30 responders at follow-up. The authors suggested that suppression of active disease by effective early treatment with sulfasalazine resulted in beneficial long-term outcome. In patients with JSPA, however, no difference was found between those receiving sulfasalazine or placebo in a blinded 26-week RCT.

The efficacy of leflunomide has been evaluated in a blinded RCT including 94 patients, where MTX was considered more effective than leflunomide. At 16 weeks, ACR Pedi30 was reached in 89% of those taking MTX vs. 68% taking leflunomide (p=0.02), ACR Pedi50 in 77% vs. 60%, and ACR Pedi70 in 60% vs. 43%, respectively. In an extension phase of 48 weeks, favorable responses were maintained, thus reflecting a sustained effect of both drugs. Improvement rates in both treatment groups were unexpectedly high, which was suggested to be associated with an early stage of disease (median disease duration 4 months). The safety profile of MTX was better during the initial 16 weeks, although liver function abnormalities were less frequent in those on leflunomide. A noncontrolled open-label study was performed on 27 JIA patients with a history of MTX failure. Of the 63% of patients completing the study at 26 weeks, 52% were ACR Pedi30, 44% ACR Pedi50, and 19% ACR Pedi70 responders. In an extension phase (9 completing), ACR Pedi30 response was observed in 56% at both 1- and 2-year follow-ups. Reversible elevation of liver function tests was noted in 11%.

No controlled studies on cyclosporine A (CSA) have been published. Ostensen et al. noted that with CSA treatment, disease activity remained virtually unchanged, and 78% of 14 patients discontinued CSA due to inefficacy or AEs. A few studies have suggested a beneficial effect of CSA, mainly in combination with MTX. Ravelli et al. reported ACR Pedi30 improvement with a combination of MTX and CSA in 47% of 17 MTX-failures. In an open-label trial, in which 83% of 41 patients had sJIA, one-third discontinued CSA due to inefficacy or AEs, and one-fourth due to remission. Side-effects were common (hypertrichosis, increased serum creatinine, hypertension, gastrointestinal symptoms, gingival hyperplasia), but usually reversible. CSA reduced systemic symptoms.
and spared glucocorticoids, but had no measurable efficacy on arthritis or uveitis. A retrospective review included 329 patients (half with sJIA) receiving CSA, given in combination with MTX in 61% of patients and in conjunction with systemic prednisolone in 65%. At the last follow-up visit, 9% of patients were in remission and 61% had moderate or severe disease activity. The reasons for discontinuing CSA were inefficacy in 61% of patients, side-effects in 22%, noncompliance in 9%, and inactive disease in 10%. The overall efficacy profile of CSA was less than satisfactory as a monotherapy and as a combination therapy, at least compared with MTX monotherapy.

A controlled 16-week blinded study of azathioprine in 32 JIA patients did not find a significantly greater effect than placebo. By contrast, in an uncontrolled trial, Savolainen et al. suggested that azathioprine did have a beneficial effect in 129 patients, of whom 38% completed a 2-year follow-up with significant improvement in disease activity, and 29% achieved remission at least temporarily. In a retrospective review of 24 children, 63% showed some clinical improvement and 38% achieved clinical remission during a mean treatment time of 13 months. Apart from reversible leucopenia leading to treatment termination, also more serious AEs have been observed.

In small patient series in refractory sJIA, beneficial effect of thalidomide as single therapy and cyclophosphamide as single drug or in combination with MTX was reported. In refractory JIA, chlorambucil was suggested to be effective, but a high mortality rate (6%) and a risk for leukemia has prevented its further use. In the most severe and life-threatening cases of progressive polyarticular and systemic JIA, autologous stem cell transplantation has been considered effective, but associated with fatal complications.

2.3.3 First-line and second-line therapy in uveitis

First-line standard therapy for anterior uveitis is topical steroids (prednisolone acetate or dexamethasone) and mydriatics, although this recommendation is based on neither randomized trials nor controlled studies. The value of prolonged corticosteroids in treating uveitis has not been thoroughly explored. Of all patients with JIA-associated uveitis, 34-41% do not respond to intensive topical treatment. Early second-line immunomodulatory therapy is recommended when quiescence of inflammation is not achieved with low-dose topical steroids, or if already at the initial presentation risk factors for vision loss are found. Recent studies have suggested efficacy of second-line agents such as DMARDs. Evidence for the beneficial effect of immunosuppressive treatments in chronic uveitis is based on observational studies.

Efficacy of MTX in treating childhood uveitis has been evaluated in several studies. In a noncontrolled study, 6 of 7 patients starting MTX had reduced inflammatory activity of uveitis, and glucocorticoid sparing was also noted. A retrospective study reviewed patients with chronic anterior or intermediate uveitis (none with JIA). During MTX therapy, in 9 of 10 children, the AC inflammation was diminished and/or the need for topical steroids decreased. Authors of another retrospective analysis suggested that initiating MTX treatment led to a remission of JIA-associated uveitis in 88% of 25 patients,
although some patients flared after discontinuing MTX. Heiligenhaus et al. observed quiescent uveitis in 71% of patients taking MTX either with (n=21) or without (n=4) topical steroids, but 20% required additional immunosuppressive medication.

CSA has been used to treat uveitis either as a monotherapy or in combination with other DMARDs. Kilmartin et al. retrospectively reviewed the charts of 14 patients with noninfectious childhood uveitis, 3 of whom had JCA. The report did not specify which patients received CSA as a monotherapy or in combination, but nevertheless suggested CSA to be effective and well-tolerated. A prospective open-label study of JIA patients included 7 patients with uveitis. The AC inflammation decreased in 4 (57%) of them, but CSA had to be discontinued in 3 patients due to inefficacy.

Reports on the efficacy of chlorambucil in refractory uveitis have been controversial. One report evaluated the impact of mycophenolate mofetil, initiated in 25 JIA patients, and described the ocular inflammation to be controlled in 36%.

### 2.4 Biologic agents in JIA and associated uveitis

#### 2.4.1 Early effective treatment?

Approximately 30-40% of JIA patients do not achieve a response of ACR Ped30 on DMARDs, although in some reports the responder rates to early DMARD therapy are somewhat higher. Moreover, in roughly 20% of those with JIA-associated uveitis, ocular inflammation is not controlled by conventional therapy. No improvement criteria for uveitis is included in the ACR or ACR Pedi criteria. Measures to evaluate the activity of uveitis have been recently standardized but are not universally followed. Refractory patients with constantly active disease have the highest risk for developing irreversible joint damage, permanent disability, and ophthalmic complications. Several therapeutic approaches have been proposed for these patients, including parenteral administration of higher doses of MTX, switching to other second-line agents (alone or in combination), or administration of third-line therapy; biologic agents.

Whether the ACR Ped30 improvement is clinically sufficient in JIA is questionable. During the 21st century, the goal of treatment has shifted from ‘satisfactory improvement’ to complete disease control. The reported rate of JIA patients achieving clinical remission on and/or off medication in arthritis varies from 11% to 26% with DMARD therapy, depending on drug and the follow-up period. There is some evidence in RA suggesting that an initial therapy with anti-TNF agents, compared with DMARDs, results not only in more rapid disease control, but also more often in clinical remission later in the course of the disease. In JIA, no such evidence is yet available.

Based on investigations demonstrating superior outcomes in RA in those receiving early treatment, many rheumatologists believe that a therapeutic ‘window of opportunity’ exists early in the disease when therapies are more effective than later on, yielding better outcomes such as clinical remission on/off medication or halting of disease progression.
A number of studies in RA and some in JIA have demonstrated an alteration of disease course with a higher responder rate, less joint damage, or improved outcome in patients starting early treatment. To establish the concept “the earlier, the better”, specific trials showing time-dependent optimal response are still needed. In JIA, no published studies on early aggressive combination therapy or early biologic therapy exist.

2.4.2 Cytokine network in rheumatic inflammation and uveitis

Overexpression of various cytokines has an important role in joint inflammation and in damage to articular tissue. Inflammatory synovitis in JIA is similar to that seen in RA, showing angiogenesis, cellular hyperplasia, inflammatory leukocytes, and changes in the expression of cell-surface adhesion molecules, proteinases, proteinase inhibitors, and many cytokines. Various mononuclear cells in subsynovial tissues include T cells, B cells, macrophages, dendritic cells, and plasma cells. T cell infiltrates are composed predominantly of Th1 type, CD4+ cells, which are important activators of macrophages.

The prolonged inflammatory process in the synovium leads to a formation of pannus, which is a tissue predominated by mononuclear cells and aggressive fibroblast-like (type B) synoviocytes. Pannus cells migrate over the underlying cartilage and into the subchondral bone, which causes erosions of these tissues. In response to pro-inflammatory cytokines, such as interleukin-1 (IL-1) and TNFα, activated pannus macrophages and fibroblast-like synoviocytes produce degradative enzymes, matrix metalloproteinases (Figure 2). Another important group of extracellular matrix-degrading enzymes are cathepsins B, K, and L, which are thought to contribute significantly to the joint damage in rheumatic inflammation. Bone destruction is mainly caused by osteoclasts. In RA, the synovial fluid consists of large amounts of receptor activator of nuclear factor kappa B ligand (RANKL). Activated synovial fibroblasts secrete RANKL at the site of invasion.

Figure 2 Simplified representation of interaction between cells of the immune system and synovial fibroblasts mediating joint destruction. IL = interleukin, TNF = tumor necrosis factor, CXCL12 = stromal cell derived factor 1α. Modified and reprinted with kind permission of Immunology Letters (Karouzakis et al. 2006;106:8-13).
Quantitative analysis suggests that there are few T cell derived cytokines (such as IL-2, IL-17, and interferon-γ) in inflamed synovial tissue, but large quantities of TNFα and IL-1 in both synovial tissue and synovial fluid. Already in 1991, evidence existed that in RA TNFα was locally produced in the lining and deeper layers of the synovium by cells of monocyte/macrophage lineage, and that affected chondrocyte metabolism led to cartilage degradation. Today, TNFα and IL-1 are known to be powerful in vitro stimulators of synovial tissue effector functions, including proliferation, metalloproteinase and adhesion molecule expression, secretion of other cytokines, and prostaglandin production. IL-6 is markedly increased in synovial tissue and fluid, and induces bone destruction through regulating T lymphocyte production of key osteoclastogenic cytokines and inflammation-induced bone marrow osteoclast differentiation. Pro-inflammatory cytokines also induce chondrocytes to produce several other proinflammatory cytokines, including IL-17, IL-18, leukemia inhibitory factor (LIF), and chemokines.

Several studies have assessed blood and synovial cytokine concentrations in different JIA subtypes, but results have been inconsistent. The reported therapeutic effect of agents inhibiting TNF supports the important role of this specific cytokine in rheumatic diseases (Figure 3).

Patients with sJIA seem to have a different inflammatory profile and treatment response than other JIA subtypes and even those with adult-onset Still’s disease. Those with sJIA show no signs of lymphocyte-mediated antigen-specific immune responses, but activation of innate immunity appears to be more important. Recent studies have documented that IL-1β, IL-6, IL-18, and phagocyte-specific calcium binding proteins (calgranulins), known as S100 proteins (S100A8, S100A9, S100A12), correlate with disease activity and secondary complications of sJIA. The overproduction of IL-6 correlates with joint involvement and may also explain many extra-articular manifestations, including microcytic anemia and growth failure. This has led many researchers to suggest that sJIA is an IL-6 mediated disease.

A controlled study on the cytokine profile in JIA-associated uveitis has been performed. Compared with controls, those with uveitis had increased levels of, for example, IL-2, IL-6, IL-10, IL-13, IL-18, IFN-γ, and TNFα in samples of the aqueous humor. IL-8 and IL-10 levels were lower in quiescent uveitis and in those taking MTX, than in active ophthalmologic inflammation and in those not treated with MTX. No significant differences in samples were found in those with or without topical or systemic corticosteroids. The authors concluded that in children with uveitis multiple cytokines, chemokines, and soluble adhesion molecules were increased in the aqueous humor regardless of active or quiescent inflammation. In another controlled study, aqueous humor and sera of patients with uveitis showed higher levels of TNFα than those of controls without uveitis, but TNFα levels were higher in the sera than in the aqueous humor. Higher serum TNFα levels were associated with recurrent uveitis. Authors suggested that TNFα participates actively in the pathogenesis of clinical uveitis, although it seems to have greater systemic than local effects.
In animal models, experimental autoimmune uveoretinitis was shown to be a CD4+ Th1-mediated disease.\textsuperscript{211} A chronically activated T cell is capable of activating neighboring cells to produce not only TNFα, but also IL-1 and IL-6, chemokines such as IL-8 and macrophage inhibitory factors, and matrix metalloproteinases. In the model, increased tissue concentrations of TNF facilitate T cell effector responses and macrophage activation, which are responsible for tissue damage and can be suppressed by anti-TNF therapies. The ability to suppress disease experimentally has led the way to clinical studies in uveitis.\textsuperscript{211}
2.4.3 Biologic agents in JIA

During the last decade, a number of well-characterized monoclonal antibodies and recombinant human molecules (e.g. cytokines, cytokine receptors, cytokine inhibitors) directed against defined endogenous target molecules have been available. Besides investigating disease mechanisms, simultaneous in vivo studies have facilitated development of improved therapies. Specific targets of biologic agents have raised hope that AEs would be less problematic than in those receiving conventional treatment, which have broader immunomodulatory effects. However, some AEs during biologic therapies have not been anticipated. A disaster occurred during a phase 1 trial with an anti-CD28 monoclonal antibody, necessitating intensive care of several subjects due to multi-organ failure induced by cytokine release syndrome. Thus, especially in children, new treatments must be used with caution, and pediatric studies should be initiated only after broad toxicity and safety analyses in vivo. In children’s short- and long-term studies, effects on growth, maturation, reproduction, cognitive functions, and emotional and psychological aspects should be evaluated. Moreover, pharmacokinetics need to be assessed separately in children due to potentially marked differences compared to adults.

Anti-TNF agents etanercept, infliximab, and adalimumab

TNF is a pivotal cytokine in the pathogenesis of rheumatic inflammation. The first reports on TNFα were published in the mid-1980s, and already in 1989 anti-TNFα agents were suggested as potential treatment options for RA. It was not until 1993 that a therapeutic trial by Elliot et al. demonstrated that TNF-inhibiting with anti-TNF had a dramatic and rapid beneficial effect on patients with RA. This trial was followed by multiple other placebo-controlled RCTs in RA patients, in which anti-TNF agents combined with MTX demonstrated an ACR20 response in 56%-72% of patients, ACR50 response in 39%-55%, and ACR70 response in 19%-27%. During the recent years, consensus statements on the use of biologic agents in rheumatic diseases have been regularly updated.

Only after larger safety and toxicity assessments in adults, were pediatric trials initiated. The first case report on a patient with sJIA receiving TNF inhibitor was published in 1997, but in 2000 the efficacy of a soluble TNF receptor on polyarticular JIA was finally demonstrated. Since then a few RCTs and some open-label pediatric trials have been reported.

Anti-TNF agents in children seem to be well-tolerated, but pooled long-term safety analyses are not yet available. Clinical experience in adults has provided data that can be adapted to children with long-term biologic therapies. Some cases of reactivated tuberculosis, opportunistic infections, demyelinating diseases, macrophage activation syndromes and lupus-like reactions have occurred in children receiving anti-TNF therapies. Neither in these conditions nor in the frequency of severe infections and malignancies has a markedly increased risk been observed during anti-TNF therapies compared with conventional treatments. Currently, until more safety data have been published, biologic agents are reserved for children with refractory JIA. Nevertheless, patients most
likely to respond and less likely to experience serious complications should be identified using registry-based data. Moreover, cost-efficacy analyses are few and have provided somewhat conflicting results. Although direct costs of biologic treatment are much higher than those of conventional therapies, the overall costs may be reasonable in the light of improved outcome and reduced indirect costs. Anti-TNF agents bind to TNFα, decreasing its bioavailability. Today, three anti-TNF agents are available for clinical use.

**Etanercept** is a recombinant form of the p75 TNF receptor coupled to the Fc fragment of human IgG1. Etanercept neutralizes TNF by binding to TNFα and may exert its effect by binding other cytokines, including IL-1α and TNFβ. It is administered twice weekly, one dose being 0.4 mg/kg (max 25 mg) sc. Lovell et al. conducted the first placebo-controlled RCT in 69 refractory JIA patients, 74% of whom achieved ACR Pedi30 at 3 months. At the end of the 2-year extension phase, 43 patients (74% from the original group) were still enrolled, and ACR Pedi30, 50, and 70 were achieved by 81%, 79%, and 67%, respectively, showing sustained efficacy. In a 4-year follow-up, the efficacy was higher; 94% of the 32 patients improved up to ACR Pedi30, and 78% up to ACR Ped70. In the 8-year open-label trial, ACR Pedi70 response or higher was recently reported in all 26 patients. Currently the only registry-based publication of anti-TNF agents in children is from a German etanercept registry, in which ACR Pedi30 was achieved at 6 months by 83% of the 322 JIA patients, and at 30 months by more than 50% of non-systemic patients. Two noncontrolled studies have evaluated the efficacy of etanercept in ERA and JSPA, and the response has been promising. Etanercept seems, however, to be less effective in sJIA than in other JIA subtypes.

**Infliximab** is a chimeric, partly humanized monoclonal TNFα antibody, which binds both soluble and cell-bound TNFα, and may enhance its effect by deleting TNFα-producing T cells through apoptosis. Infliximab is administered as iv infusions of 3-6 mg/kg at 6- to 8-week intervals after loading doses at baseline and at 2 weeks. The efficacy of infliximab in JIA or JSPA has been documented in small open-label studies, and finally in 2007 in a RCT. Although a nonsignificant between-group difference was observed during the placebo-controlled phase, results were consistent with a favorable risk/benefit profile in adults. In one year, 73% of 122 JIA patients achieved ACR Pedi30, 70% ACR Pedi50, and 52% ACR Ped70. AEs occurred less often in those receiving a dose of 6 mg/kg compared with 3 mg/kg, although in the efficacy no significant difference between the doses was demonstrated. Preliminary data of a blinded RCT in JSPA during a 3-month trial suggest that in 12 patients receiving infliximab compared with 14 patients receiving placebo, inflammatory signs and symptoms decreased significantly (p=0.007). AEs were comparable in both treatment groups. Of JIA patients receiving infliximab, approximately 20% had infusion-related reactions, leading to treatment discontinuation. Adverse drug reactions and loss of efficacy with infliximab treatment may be associated at least partly with the development of anti-chimeric antibodies. Thus, no data are available on the long-term efficacy of infliximab, on long-term comparisons between etanercept and infliximab therapies, or on switching between these agents.

**Adalimumab** is a humanized IgG1 anti-TNFα monoclonal antibody that blocks interaction with the p55 and p75 cell-surface TNFα receptors. No studies on JIA patients have been published. In a long-term study on RA, adalimumab has shown sustained
efficacy. Highly promising pilot data on a blinded RCT have been reported for adalimumab, administered at a dose of 24 mg/m² (ad 40 mg) every other week. At week 16, 84% of patients achieved ACR Pedi30, 77% ACR Pedi50, 58% ACR Pedi70, and 27% ACR Pedi90. During a placebo-controlled phase, significantly more patients in the placebo than in the adalimumab group flared. Of 128 patients entering the trial, 75% completed the 2-year follow-up. Their ACR Pedi30, 50, 70, and 90 responses were sustained up to 2 years (94%, 93%, 81%, and 60%, respectively) and were comparable in patients with and without MTX.

**Other biologic agents**

When JIA patients do not respond to TNF blockers, other biologic agents may provide therapeutic options. Only a few pediatric reports have been published, but several trials are ongoing. Encouraging reports on the substantial clinical improvement seen in patients with sJIA receiving anti-IL-1 or anti-IL-6 therapies support the hypothesis that the key mediators of sJIA are these cytokines instead of TNFα. Larger safety analyses on pediatric patients are not yet available. Based on adult trials, avoiding the use of anti-TNF therapies in combination with other biologic agents is recommended due to the increased risk of infections. Biological agents are usually combined with MTX to achieve better clinical results.

**Anakinra**, a recombinant IL-1 receptor antagonist (IL-1RA), is administered as daily sc injections of 1-2 mg/kg (ad 100 mg daily). A couple of case series of refractory sJIA patients have been published, suggesting favorable responses in 7 of 9 and 6 of 7 patients. However, pilot data on anakinra in juvenile polyarthritis demonstrated no efficacy compared with placebo. A recent investigation compared patient response to anakinra in sJIA and adult-onset Still’s disease. While 73% of 15 adults achieved ACR50 improvement, only 25% of 20 juveniles showed a comparable improvement. Whereas the IL-1 blockade has a dramatic and sustained effect in some sJIA patients, many others are partial responders or nonresponders, suggesting a different disease pathogenesis that is more independent of IL-1 pathway.

In children with sJIA, blockade of IL-6 signaling has been reported to be more effective than treatment with IL-1 blockade. Because IL-6 is able to be stimulated by both the IL-1 and TNF pathways, it is suggested that IL-6 blockade will take care of processes in both pathways. Tocilizumab, also called MRA, is a humanized antihuman IL-6 receptor antibody of the kappa-IgG1 subclass, designed using genetic engineering technology. Tocilizumab recognizes both membrane-bound and soluble forms of human IL-6 receptor, thus inhibiting the binding of IL-6 to its receptor and its pro-inflammatory activity. It is administered as iv infusions, and in a phase III trial the dose was 8 mg/kg every 2 weeks. In a phase II trial, after three infusions 91% of 11 sJIA patients reached ACR Pedi30. Thus far published only as an abstract, the subsequent trial with a 6-week open-label phase showed ACR Pedi30, 50, and 70 improvement in 91%, 86%, and 68% of 56 sJIA patients. Next, 43 patients entered a 12-week double-blind phase, in which tocilizumab proved to be more effective than placebo. Tocilizumab is not yet in wider use. Its short-term safety
reports are promising, and its long-term tolerability is currently being evaluated in an extension study. In RA, long-term tolerability and efficacy have been good, but warrant further investigations.\textsuperscript{242}

T cell activation requires antigen presentation by antigen-presenting cells (dendritic cells, macrophages, or activated B cells) and co-stimulation, such as via CD80 or CD86. The two molecules bind to CD28 on T cells, but have higher affinity to cytotoxic T lymphocyte antigen 4 (CTLA 4), which is expressed on the T cell after activation and mediates T cell downregulation. \textit{Abatacept} is a recombinant fusion protein, consisting of the extracellular domain of human CTLA 4 and part of the Fc domain of human IgG1. This CTLA 4 immunoglobulin molecule inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28.\textsuperscript{238} During a 4-month open-label phase of an ongoing pediatric trial, 65\% of 170 JIA patients achieved ACR Pedi30, and abatacept was effective in all JIA subtypes: in 68\% of seropositive polyarthritis, 64\% of seronegative polyarthritis, 65\% of sJIA, and 59\% of extended oligoarthritis. One-third of patients had previously experienced failure with anti-TNF agents, and in these patients ACR Pedi30, 50, and 70 responder rates were 39\%, 25\%, and 11\%, respectively. One patient had leukemia, but according to researchers this was unlikely to be related to abatacept. Abatacept was well-tolerated in this pilot study.\textsuperscript{243}

\textit{Rituximab} is a chimeric human/mouse monoclonal antibody directed at the CD20 antigen expressed on mature B and pre-B cells. It specifically depletes CD20+ B cells via several mechanisms and has long been approved for treatment of CD20+ non-Hodgkin’s lymphoma.\textsuperscript{238} Apart from anecdotal reports, no published evidence on the efficacy of rituximab in JIA exists. In RA, rituximab is used for anti-TNF failures.\textsuperscript{244}

Various novel targets are currently being investigated, such as IL-15, 17, 18, and 32, chemokines or chemokine receptors, Toll-like receptor pathways, and janus-kinase/signal-transducer and activator of transcription (Jak/STAT) pathways. Several compounds are under phase I-III trials in adults; pediatric trials have not yet been conducted. The latest TNF inhibitors are \textit{certolizumab pegol}, a pegylated Fc free anti-TNF agent, and \textit{golimumab}, a human monoclonal TNF\textsubscript{a} antibody. An older target, IL-1, is still of interest. \textit{Rilonacept}, a long-acting IL-1\textbeta inhibitor, and \textit{AMG}, a human monoclonal antibody to IL-1R, are being investigated. \textit{Denosumab} is a humanized IgG monoclonal antibody binding to RANKL, which interferes with osteoclast activation. Denosumab has been found to inhibit bone erosions without affecting disease activity. Inhibition of cathepsin K may also interfere with the erosive process.\textsuperscript{238}

\subsection*{2.4.4 Biologic agents in JIA-associated uveitis}

Anti-TNF treatment has shown promise in the treatment of JIA-associated uveitis, although almost all studies concerning children are noncontrolled and patient series are small. A meta-analysis of the impact of anti-TNF therapy on anterior uveitis in ankylosing spondylitis and data collected from placebo-controlled and open-label studies have recently been published.\textsuperscript{245} The overall exposure to placebo was 71 years in 170 patients and to anti-TNF agents 146 years in 297 patients on etanercept and 90 patients on infliximab. The
frequency of flares of anterior uveitis during placebo vs. anti-TNF treatment was 15.6 vs. 6.8 per 100 patient-years (p=0.01). The flares were less frequent during infliximab than during etanercept treatment. Paradoxically, it has also been suggested that etanercept causes uveitis. Analysis of US registries revealed that etanercept therapy was associated with a significantly greater number of reported uveitis cases than infliximab or adalimumab. In adults, infliximab has a documented efficacy especially in uveitis related to Bechter’s disease.

A few studies have evaluated the efficacy of etanercept, a soluble TNF receptor, on uveitis in children. A retrospective report of 3 JIA patients, a randomized placebo-controlled trial (n=12), and a questionnaire-based survey failed to show a treatment effect. On the contrary, a mild improvement of ocular inflammation during etanercept therapy was found in 60% of 10 children up to 3 months, and in 40% up to one year.

In USA and most of Europe, infliximab, a monoclonal TNFα antibody, is not used off-label in children, and until recently, publications have been few. In retrospective studies with 6 JIA patients in each series, a suppression of ocular inflammation was documented. Kahn et al. observed significant improvement in the inflammatory activity of chronic uveitis in 100% of 17 children (59% with JIA) during high-dose infliximab treatment of 10-20 mg/kg with 1-7 infusions. During a mean follow-up of 14 months (range 3-34 months) without serious AEs, all reached quiescent uveitis. Topical steroids were discontinued in 15 patients (88%).

Two reports suggest that adalimumab, a humanized monoclonal TNFα antibody, has a favorable effect on childhood uveitis. In a retrospective analysis of 18 patients (94% with JIA), adalimumab was suggested to control effectively uveitis in 88%. Another open-label study on 14 children, 64% who had JIA-associated uveitis and 36% idiopathic uveitis, demonstrated decreased AC cellular flare in 81%, sustained resolution of inflammation in 65% and worsening in 3% of 26 affected eyes.

Some studies in children have analyzed larger patient series or compared anti-TNF agents. Infliximab in 13 children resulted in better clinical improvement than etanercept in 11 children, reviewed in a retrospective study with heterogeneous patient sample (57% with JIA-associated uveitis). Based on retrospective review on 1109 JIA-patients, the risk for new-onset uveitis is comparable in patients with or without anti-TNF treatment. Although new-onset uveitis occurs more frequently in those receiving etanercept than infliximab, this difference has not been shown to be statistically significant. In a questionnaire-based survey concerning 47 JIA patients with uveitis, good response was observed in 47% of 34 patients on etanercept, in 68% of 25 patients on infliximab and in 100% of 3 patients on adalimumab.

In adults, dacilizumab, a humanized monoclonal antibody against the IL-2 receptor, administered as iv infusions, has shown favorable effects in the treatment of posterior uveitis, but a recent small placebo-controlled RCT revealed no benefit. The efficacy of dacilizumab, anakinra, or rituximab in JIA-associated uveitis remains unclear.

Although biologic therapies have been proven effective by RCTs in JIA, a similar strength of evidence is lacking for uveitis. It is vital that research networks be established to facilitate RCTs so that in the future the treatment of JIA-associated uveitis is evidence-based.
3 AIMS OF THE STUDY

The aim of the present investigation of anti-TNF therapies in children with JIA and JIA-associated uveitis was to evaluate the safety, efficacy, and drug survival with anti-TNF therapies etanercept, infliximab, and adalimumab in real-life clinical practice.

More specifically, the study objectives were as follows:

1. To evaluate the impact of anti-TNF treatment on growth velocity and bone maturation in refractory JIA (I).
2. To identify the predictors of the change in growth velocity during anti-TNF treatment (I).
3. To assess the impact of first-line biologic therapies etanercept and infliximab on JIA-associated uveitis (II).
4. To evaluate the efficacy of adalimumab, a second-line anti-TNF treatment, in JIA-associated uveitis, especially in patients refractory to first-line therapy (III).
5. To evaluate long-term drug survival with anti-TNF agents and predictive factors for discontinuation of treatment in patients with JIA and JIA-associated uveitis (IV).
4 PATIENTS AND METHODS

4.1 Subjects (I-IV)

The study population consisted of JIA patients classified based on revised ILAR criteria\(^{27}\) and JIA patients with chronic anterior uveitis (II, III) defined according to SUN criteria\(^{107}\) (Figure 4, Table 5). The follow-up of patients took place at the Department of Pediatrics in three tertiary centers: the Hospital for Children and Adolescents, Helsinki (I-IV); the Rheumatism Foundation Hospital, Heinola (I-IV); and the Oulu University Hospital (I, IV).

To evaluate growth during anti-TNF treatment (I), patients aged less than 15 years at anti-TNF onset and who had received anti-TNFs for over a year (mean 23.1 months, range 13-24) were included. Of these patients, 43 were taking etanercept and 28 infliximab. Adolescents who had already reached their final height were excluded, as well as were all of those who had received GH previously or had ongoing GH treatment.

![Figure 4](image-url)  
Enrollment and follow-up (F/U) of JIA patients in three tertiary centers of pediatric rheumatology during 2002-2007 (I-IV).
Of 108 patients (II), 95% received anti-TNF therapy since 1999-2001 due to arthritis and 5% due to refractory uveitis. Two uveitis patients were excluded from the final analyses because the onset of uveitis occurred after discontinuation of anti-TNF therapy (Figure 5).

In the study on adalimumab (III), 19 of 20 patients had experienced failure in previous biological treatment due to inefficacy (11/11 on etanercept, 13/18 on infliximab) or side-effects (5/18 on infliximab).

To evaluate long-term drug treatment survival in the whole cohort (IV), patients aged <16 years at first anti-TNF treatment and with at least a one-year follow-up completed by the end of year 2005 were included. Mean follow-up with either etanercept (n=105) or infliximab (n=104) treatment was 30 months (SD ± 21 months, range 1 to 97). Patients who did not fit into any JIA category, or were ≥ 16 years at anti-TNF onset were excluded.

4.1.1 Drug therapy

All patients were unresponsive to previous single or combination DMARDs. The decision to start biologic agents was at the discretion of the pediatric rheumatologist in charge. Before 2003, the supply of etanercept was limited, and juvenile patients received off-label infliximab and later adalimumab. Anti-TNF therapy was initiated on top of concomitant DMARDs. During follow-up, DMARDs and oral prednisolone were tapered if neither arthritis nor increased ocular inflammation had occurred. Concomitant MTX was given 10-20 mg/m² up to 35 mg weekly when no limiting side-effects emerged. Other DMARDs, such as sulfasalazine, CSA, azathioprine, or hydroxychloroquine, were chosen instead of MTX or in combination with MTX when necessary.

Local therapy of uveitis included topical corticosteroids and mydriatics, and immunosuppressive therapy was most often started with MTX and/or CSA and/or oral prednisolone before the initiation of biologic agents (II, III).
Table 5  Characteristics of JIA patients concerning drug survival (IV), growth (I), and uveitis (II, III) with the biologic agents (BA) of etanercept (ETA), infliximab (IFX), or adalimumab (ADA). Data are expressed as number (%) or mean (±SD).

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Drug survival (IV)</th>
<th>Growth (I)</th>
<th>Uveitis ETA / IFX (II)</th>
<th>ADA (III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>209</td>
<td>71</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Type of JIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seronegative polyarthritis</td>
<td>104 (50)</td>
<td>45 (63)</td>
<td>27 (60)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Seropositive polyarthritis</td>
<td>9 (4)</td>
<td>3 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extended oligoarthritis</td>
<td>42 (20)</td>
<td>19 (27)</td>
<td>14 (31)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Persistent oligoarthritis</td>
<td>16 (8)</td>
<td>0</td>
<td>3 (7)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Systemic JIA</td>
<td>13 (6)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Enthesitis related arthritis</td>
<td>21 (10)</td>
<td>2 (3)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>4 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Uveitis</td>
<td>75 (36)</td>
<td>27 (38)</td>
<td>45 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>ANA-positive</td>
<td>88 (42)</td>
<td>31 (44)</td>
<td>29 (64)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>HLA-B27 present</td>
<td>70 (33)</td>
<td>27 (38)</td>
<td>15 (33)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Age at onset of BA (years)</td>
<td>10.1 ± 3.5</td>
<td>9.6 ± 3.2</td>
<td>10.0 ± 3.1</td>
<td>13.5 ± 3.3</td>
</tr>
<tr>
<td>Duration of JIA (years)</td>
<td>5.8 ± 3.4</td>
<td>5.0 ± 3.6</td>
<td>7.1 ± 3.5</td>
<td>10.1 ± 3.5</td>
</tr>
<tr>
<td>Onset of JIA (years)</td>
<td>5.1 ± 3.5</td>
<td>3.8 ± 2.8</td>
<td>2.9 ± 2.0</td>
<td>3.4 ± 2.1</td>
</tr>
<tr>
<td>No. of DMARDs at baseline</td>
<td>2.1 ± 1.0</td>
<td>2.3 ± 1.0</td>
<td>2.3 ± 1.0</td>
<td>2.3 ± 1.0</td>
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<tr>
<td>No. of active joints at baseline</td>
<td>8 ± 8</td>
<td>10 ± 9</td>
<td>7 ± 7</td>
<td>10 ± 9</td>
</tr>
<tr>
<td>Prednisolone (mg/kg) at baseline</td>
<td>0.2 ± 0.4</td>
<td>0.2 ± 0.2</td>
<td>0.2 ± 0.2</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>ESR at baseline (mm/hr)</td>
<td>29 ± 24</td>
<td>32 ± 21</td>
<td>32 ± 23</td>
<td>32 ± 21</td>
</tr>
<tr>
<td>CRP at baseline (mg/l)</td>
<td>23 ± 34</td>
<td>23 ± 25</td>
<td>19 ± 23</td>
<td>23 ± 25</td>
</tr>
</tbody>
</table>

In the study on growth (II), we assessed total corticosteroid exposure. All doses during the four-year follow-up (oral, intra-articular, iv) were summed. Different types of corticosteroids were converted into approximate prednisolone equivalents based on their glucocorticoid or anti-inflammatory properties, using the following equation: 4 mg methylprednisolone = 4 mg triamcinolone = 5 mg prednisolone = 0.75 mg betamethasone = 6 mg deflazacort.262

Initial etanercept dose was 0.4 mg/kg twice weekly sc (I, II, IV). Infliximab was given 80-200 mg (3-6 mg/kg) iv, initially at 2-, 4-, and 6-week intervals and later, based on response of arthritis and/or uveitis, every 4-8 weeks or every 12 weeks (I, II, IV). Patients taking adalimumab (III) received a standard dose of 40 mg (0.6-1.5 mg/kg) sc every two weeks. Two patients weighing less than 30 kg initially received 20 mg every two weeks.
4.2 Methods

All patient charts were reviewed retrospectively (I-IV). Alongside clinical work, part of the data were collected prospectively concerning growth velocity and bone age during 2003 (I), or the efficacy assessment of adalimumab during 2003-2005 (III).

4.2.1 Assessment of growth and skeletal maturation (I)

Growth measurements were recorded for four years (two years before and two years from the onset of anti-TNF agents). A pediatrician or nurse measured children’s height and weight, which were recorded on Finnish growth charts. Height standard deviation score (HSDS), comparable to height Z-score, was defined as deviation of height, in SD units, from mean height for chronologic age and gender. Growth velocity was defined as a change in HSDS (ΔHSDS) during the follow-up; positive indicating catch-up growth and negative impaired growth. Weights were expressed according to Finnish standards as relative weight, i.e. height-adjusted weight, as percentages from the mean ratio in the normal population of the same gender and height. Body mass index (BMI) was calculated as weight (kg) divided by height² (m²).

An experienced pediatric radiologist determined skeletal maturation using the Greulich-Pyle method in relation to measurements in Finnish children. Normal bone age was determined between ± 1 SD based on each patient’s calendar age and gender. Bone age was assessed prior to anti-TNF therapy and two years after initiation of therapy.

For comparative purposes, patients were divided into two categories based on growth velocity (ΔHSDS) for two years before commencement of anti-TNF therapy: those with delayed growth (ΔHSDS < 0) and those with normal or accelerated growth (ΔHSDS ≥ 0).

Parental heights were obtained from patient charts, and midparental target height (V) was calculated as follows: 0.0611 x father’s height (cm) + 0.0703 x mother’s height (cm) - 22.37.

4.2.2 Criteria for disease activity in JIA (I-IV)

Inactive disease and clinical remission were defined based on international guidelines. A pediatric rheumatologist examined the patients every 8-24 weeks (I-IV), depending on the activity of the disease. At each visit, the number of active and swollen joints, ESR, CRP, and laboratory tests for drug safety were assessed (I-III). Physician’s VAS, parents’/patient’s VAS, and CHAQ were evaluated. Improvement of arthritis during adalimumab (III) was assessed by ACR Pediatric criteria.

For comparative purposes (IV), we decided to divide patients into two categories (high or moderate) according to baseline disease activity parameters. High activity was defined as ≥ 3 of the following: patients with ≥ 5 active joints or erosive arthritis, CRP ≥ 40 mg/l, ESR ≥ 30 mm/hr, number of DMARDs ≥ 2, prednisolone ≥ 0.3 mg/kg, sight-threatening
uveitis with macular edema, and/or activity of uveitis ≥ grade 3+. Moderate activity was defined as patients with increased disease activity, but less than in those with high activity.

**4.2.3 Evaluation of uveitis (II, III)**

Based on current guidelines, an ophthalmologist examined all JIA patients every 3-4 months (< 7 years of age), yearly (7-12 years), or every 1-2 years (> 12 years). Those with uveitis were examined every 2-12 weeks, depending on the activity of uveitis, including BCVA (range from 0-1.0), biomicroscopy of the anterior segment of the eye, and evaluation of cells and aqueous flare. Posterior parts of the eye were examined by dilated indirect ophthalmoscopy or by a Volk 90D lens. Ocular pressure was measured by applanation tonometry. Ocular complications (cataract, glaucoma, cystoid macular edema, and band keratopathy) were registered.

A flare in uveitis was defined as an episode with worsening activity in AC inflammation during follow-up (II, III). Tapering of topical steroids or concomitant immunomodulators had no influence on the evaluation of outcome. The decrease or increase in activity of uveitis was based on modified criteria, as in older recommendations (II, III)\textsuperscript{268, 269} or on SUN criteria, as in recent recommendations (III)\textsuperscript{107} (Table 6). We used these two criteria in the studies II-III due to the publication of the SUN guidelines in between data collection phases of II and III.

In the former method, an improvement was defined as a reduction of inflammation by at least one grade, and a worsened activity as increased inflammation by at least one grade, worsening of visual acuity, development of ocular complications, or a first course of uveitis during biologic therapy. If one eye improved, but in the other the activity improved, the interpretation was improved activity.

In the latter method based on SUN criteria,\textsuperscript{107} improved activity of uveitis was defined as either a two-step decrease in the level of inflammation or a decrease to inactive level (grade 0), and a worsening of the inflammation as either a two-step increase in the level of inflammation or an increase to the maximum grade (4+). If one eye improved, but the other eye worsened, the interpretation was improved activity.

<table>
<thead>
<tr>
<th>SUN criteria</th>
<th>AC cells</th>
<th>Modified criteria</th>
<th>AC cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>grade</td>
<td></td>
<td>grade</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&lt; 1</td>
<td>0</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>0.5+</td>
<td>1-5</td>
<td>1</td>
<td>3-10</td>
</tr>
<tr>
<td>1+</td>
<td>6-15</td>
<td>2</td>
<td>11-30</td>
</tr>
<tr>
<td>2+</td>
<td>16-25</td>
<td>3</td>
<td>&gt; 30</td>
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<tr>
<td>3+</td>
<td>26-50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6  
Anterior chamber (AC) inflammation in uveitis based on SUN criteria \textsuperscript{107} or modified criteria \textsuperscript{268, 269}.  

46
Baseline evaluation of ocular activity was performed when treatment with the anti-TNF agent in question commenced (II, III). In the study on etanercept and infliximab (II), the endpoint evaluation of ocular activity was performed at 24 months or at the termination of the first-line anti-TNF agent. Additionally, the number of all uveitis flares during the follow-up was recorded. The mean follow-up was 21 (SD ± 6, range 6-24) months.

In the study on adalimumab (III) as the first-line (n=1), second-line (n=9), or third-line (n=10) anti-TNF agent, the endpoint evaluation was performed either at the end of follow-up or at the termination of adalimumab. The number of flares was assessed from one year before adalimumab to baseline and from baseline to the end of follow-up. The mean follow-up was 19 (SD ± 10, range 5-36) months. For comparative purposes, we evaluated AC inflammation with both modified and SUN criteria.

4.3 Statistics (I-IV)

Results were reported as mean or median with 95% confidence intervals (CI) or interquartile range, respectively, and in selected cases with range. The nature and distribution of each variable were the basis of choosing an appropriate test for assessing statistical differences. Only two-sided tests were used, and the level of significance was 5%. Differences between categorical variables were tested with Chi-square ($\chi^2$) and Fisher’s exact tests, or between dichotomous variables in related samples with McNemar’s test. In continuous variables, normality was assessed using Kolmogorov-Smirnov’s test and equality of variances with Levene’s test. In small samples (n < 30) and in those with nonnormal distribution or nonequal variances, differences between groups were compared with nonparametric tests; between two independent samples by Mann-Whitney’s U-test, between >2 samples by Kruskall-Wallis test, and between two related samples by Wilcoxon’s Signed-Rank test. Otherwise independent-samples T-test or paired-samples T-test was used for comparison. The association between variables was tested by either Pearson’s or by nonparametric Spearman’s correlation test.

More specifically, in the study on growth (I), Finnish growth charts were used as a standard mean.263, 264 The growth velocities in patients with delayed or normal growth were compared using paired samples T-test. Correlations between growth velocity and disease-related variables were assessed with Spearman’s test. The effect of glucocorticoids and disease-related variables on growth velocity was calculated by multivariate linear regression analysis.

In the study on uveitis (II), comparison of etanercept and infliximab was performed by Fisher’s exact test for the outcome of AC activity and by Mann-Whitney’s U-test for difference in the number of flares/year before and during biologic treatment.

In the study on adalimumab in uveitis (III), differences between the number of flares/year and disease activity parameters before and during adalimumab therapy were compared using Wilcoxon’s Signed-Rank and McNemar’s tests. Spearman’s correlation coefficient ($r_s$) was assessed between favorable response or change in the number of flares/year and disease-related parameters. Linear and logistic regression analyses were performed to estimate predictors or independent variables correlating with change in
number of flares and favorable outcome, respectively. Differences in patient characteristics between those with good or poor outcome on adalimumab were compared with Mann-Whitney U-test or Fisher’s exact test.

In the study on treatment survival (IV), two separate analyses were performed; the first on all patients with their first anti-TNF agent and the second focusing on patients during the second anti-TNF agent. Kaplan-Meier analyses illustrated treatment survival; i.e. continuation rates (%) while on a drug. Comparison of differences between first-line anti-TNFs were based on log-rank statistics in nonadjusted, and gender- and disease activity-adjusted models. Adjusted values were presented because some of the baseline characteristics were different between the two treatment groups. The comparison between the first and the second courses of treatment was based on McNemar's test. Predictors of treatment discontinuation were assessed by proportional hazards model (Cox's regression) using hazard ratios (HRs). Factors included in Cox models were baseline anti-TNF agent, age, duration of JIA, gender, JIA subtype, RF, ANA, HLAB27, uveitis, CRP and ESR at baseline, number of DMARDs, number of active joints, prednisolone/kg at baseline, and in analyses of the second anti-TNF, also the first anti-TNF agent and the reason for its discontinuation.

Statistical analyses were performed with SPSS 12.0 (I, II) or 14.0 (III, IV) for Windows.

### 4.4 Ethical considerations and registry aspects

Approval to keep a temporary register of JIA patients on biologic agents, including data from three tertiary centers in Finland, was granted by the Finnish Ministry of Social Affairs and Health (I-IV). Some data on drug efficacy (III) was obtained from ROB-FIN, which has been authorized by the Ethical Committee of the Helsinki University Central Hospital. To join this national registry, each patient’s parents or legal guardian and patient him/herself (if aged more than seven years and able to write) gave written informed consent.

In the beginning of data collection phase, no registry-based data on anti-TNF agents in children existed. After founding in 2005 the children’s registry for biological agents as an amendment to a formerly founded adults’ registry for biological agents (ROB-FIN), all the previously collected data appropriate to this national registry were transferred to ROB-FIN after obtaining informed consent. Long-term registries are needed to monitor the toxicity and long-term effects of biologic agents. In international consensus guidelines, national registries for biologic agents are strongly recommended.²¹⁸
5 RESULTS

5.1 Growth during anti-TNF treatment (I)

At initiation of anti-TNF treatment, of 71 patients 53 had delayed growth velocity and 18 normal or accelerated growth velocity. No significant differences existed between these two groups in baseline characteristics. At the end of follow-up, 52% of all patients had inactive disease, and in addition, in 24% of patients the number of active joints and ESR and CRP had decreased by at least 70%, in 17% by 30-69%, and only in 7% by less than 30%. In the whole group, mean ESR had decreased from 32 to 14 mm/h (p<0.001), mean CRP from 23 to 8 mg/l (p<0.001), and mean number of active joints from 10 to 2 (p<0.001). No serious AEs or side-effects were recorded.

5.1.1 Change in growth velocity (I)

For the whole group of 71 patients, a significant increase in the change in growth velocity (ΔHSDS) was observed. This change was due to the increase in ΔHSDS in the 53 patients with previously delayed growth, whose annual mean ΔHSDS increased by +0.45 (95% CI 0.33 to 0.56, p<0.001) between two years before and two years after the commencement of anti-TNF therapy. In the 18 patients with previously normal growth, mean ΔHSDS was +0.05 (95% CI -0.07 to 0.16, p=0.39). At two years of anti-TNF therapy, both HSDS and ΔHSDS (Figure 6) were comparable between these patient groups. If calculations were performed as cm/year, the increase in growth was +1.8 cm/year (95% CI 1.2 to 2.3, p>0.001) in patients with previously delayed growth.

Figure 6  Mean (95% CI) change in growth velocity (ΔHSDS) 2 years before (-2 to 0) to 2 years (0 to 2) after commencement of anti-TNF therapy in JIA patients with previously delayed or normal growth. Modified and reprinted with kind permission of Annals of Rheumatic Diseases (Tynjälä et al. 2006;65:1044-9).
Figure 7  Relationship between annual height velocity two years before and two years after anti-TNF treatment commenced. The patients in quadrant A previously had delayed growth, but experienced catch-up during anti-TNF therapy, and those in quadrant D had delayed growth velocity both before and after anti-TNF therapy. Reprinted with kind permission of Annals of Rheumatic Diseases (Tynjälä et al. 2006;65:1044-9).

Of the 71 patients, in 54 (76%) during anti-TNF treatment growth velocity improved. Of these 54 patients, 40 had previously had delayed growth, but experienced catch-up after anti-TNF treatment commenced (Figure 7, quadrant A). Their ΔHSDS was +0.59 ΔHSDS/year (95% CI 0.47 to 0.69, p<0.001, range +0.1 to +1.89). Of the remaining 17 patients, 14 (20%) had normal or accelerated growth velocity throughout follow-up (Figure 7, quadrant B), 13 (18%) had decelerated growth velocity both before and after anti-TNF treatment (Figure 7, quadrant D), and 4 (6%) had normal growth velocity before, but a decrease after the initiation of biologic drugs (Figure 7, quadrant C). Higher glucocorticoid dose together with older age and poor response to anti-TNF therapy were associated with decelerating growth velocity.

To ensure that increased growth velocity was unrelated to pubertal growth spurt, ΔHSDS was analyzed in girls aged < 7 years and boys aged < 9 years at commencement of anti-TNF therapy. Of such patients, ΔHSDS increased by +0.85 (95% CI 0.62 to 1.07, p<0.001) in 13 with previously delayed growth. Furthermore, 37 patients were prepubertal based on the observation that delayed bone age is associated with delayed pubertal development.270 Boys with bone age < 13 years and girls with bone age < 11 years were included, and in 26 (70%) with previously delayed growth, ΔHSDS increased by +0.54 (95% CI 0.35 to 0.73, p<0.001).
Height-adjusted relative weight increased significantly in patients with delayed growth from +11.2% to +15.4% (95% CI 0.7 to 7.6, p=0.018), but insignificantly (p=0.467) in those with normal growth. BMI increased significantly from 18.3 to 19.7 kg/m², and especially in patients with delayed growth by +1.5 kg/m² (95% CI 0.9 to 2.0, p<0.001). During anti-TNF treatment, seven patients, six of whom were obese before commencement of treatment (BMI > 25 kg/m² and relative weight > 40%), gained weight excessively. BMI increased by +5.3 (range 2.7-8.1) kg/m² and mean relative weight by +26% (range 12-39%). Compared with others, these obese patients had earlier onset of JIA (mean 1.7 years) and longer disease duration (mean 9.2 years).

In patients receiving etanercept vs. infliximab, ΔHSDS and changes in height-adjusted relative weight and BMI were comparable.

5.1.2 Skeletal maturation (I) and target height (V)

Bone age was measured at anti-TNF treatment initiation and two years after initiation from 24 (34%) and 63 patients (89%), respectively. In those with both measures available, the stage of skeletal maturation was comparable in 17 (71%), changed from delayed to normal in 6 (25%), and from normal to advanced in one (a girl with relatively early puberty). Thus, none had any abnormal progression of skeletal age. At two years from anti-TNF initiation, bone age was normal in 70% of the 63 patients, delayed in 27%, and advanced in 3%.

Midparental target height was available for 39 patients (Figure 8). Throughout follow-up, the difference between actual HSDS and target height persisted; the mean difference being greatest at anti-TNF initiation: -1.45 HSDS (95% CI -1.8 to -1.1, p<0.001). Growth retardation, i.e. height below -2 HSDS, was observed in 10/71 patients (14%) at 2 years before anti-TNF initiation, in 16 (23%) at initiation, and in 16 (23%) at two years after initiation. Of these patients, 7, 13, and 14 belonged to the group with delayed growth, respectively.

Figure 8 Median, interquartile range, and range of height SDS (HSDS) at -2, 0, and 2 years in relation to anti-TNF onset and midparental target height (Target HSDS) in 29 JIA patients with delayed and 10 patients with normal growth velocity. Median, interquartile range, and range are depicted as a bar, box, and whiskers, respectively, and outliers are shown as circles above or below the range (V).
5.1.3 Predictors of change of growth velocity (I)

Cumulative glucocorticoid exposure (oral, iv, and intra-articular) before and after anti-TNF therapy was carefully reviewed. No differences in steroid doses were found between patients with delayed growth and those with normal growth. During anti-TNF therapy, decrease in glucocorticoid intake was significant in both groups (p<0.001). The relationship between ΔHSDS and change in corticosteroid doses in those with delayed growth was weak (r = -0.051), and in those with normal growth moderate (r = -0.670). In linear regression analyses of all patients, the change in glucocorticoid doses had a weak age-adjusted relationship with ΔHSDS (r = -0.27 [95% CI: -0.47 to –0.04]). In those with delayed growth, this association was not significant, but in those with normal growth strong (r = -0.76 , p<0.001).

In multivariate linear regression analyses, cumulative four-year oral prednisolone (mean 4.9 g, range 0-18.0 g) and four-year intra-articular steroid dose (mean 1.4 g, range 0.1-3.9 g) were weak predictors for ΔHSDS (r = -0.33 and r = -0.26, respectively). However, the most important predictor was growth velocity prior to anti-TNF therapy (r = -0.83). Another significant predictor was ESR at two years from anti-TNF initiation, reflecting the response to therapy. However, number of active joints or CRP at any timepoint during follow-up could not predict ΔHSDS.

5.2 Anti-TNF agents in JIA-associated uveitis (II, III)

5.2.1 Occurrence of uveitis in refractory JIA (II)

The cohort of 108 refractory JIA patients, 60% of them with polyarthritis and 31% with extended oligoarthritis, was followed from 1999 to 2005. Uveitis was observed in 47 patients (44%) (Figure 5 in Methods). Two patients were excluded from final analyses because their first uveitis flare occurred after terminating anti-TNF agents. However, a comparison of patients with (n=47) and without (n=61) uveitis was performed. At anti-TNF initiation, baseline demographics were comparable, except for the lower number of active joints (7 vs. 11, p=0.003), the higher frequency of ANA positivity (63% vs. 29%, p<0.001), the younger age at JIA onset (2.8 vs. 4.8 years, p<0.001), and the longer duration of JIA (7.0 vs. 5.5 years, p=0.028) in those with uveitis.

Five patients had their first course of uveitis during anti-TNF treatment and concomitant MTX; 4 on etanercept and 1 on infliximab. At the time of first uveitis flare, etanercept doses were consistent with current recommendations, but infliximab dose was below the recommended level (2.4 mg/kg). The inflammation resolved in 10 months after doubling the infliximab dose. Occurrence of new cases of uveitis per 100 patient-years was 1.1 (95% CI 0.03 to 5.54) during infliximab therapy and 2.2 (95% CI 0.59 to 6.13) during etanercept therapy, this difference being nonsignificant (p=0.600).
Table 7  Ophthalmologic characteristics and complications in patients with uveitis receiving etanercept or infliximab (II) or adalimumab (III). Data is expressed as number (%) or mean (range) at initiation of anti-TNF therapy (baseline) or at the end of follow-up (F/U).

<table>
<thead>
<tr>
<th></th>
<th>etanercept or infliximab</th>
<th>adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Bilateral uveitis</td>
<td>34 (76)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Age at onset of uveitis (years)</td>
<td>6 (1 - 17)</td>
<td>5 (1 - 14)</td>
</tr>
<tr>
<td>Age at anti-TNF onset (years)</td>
<td>10 (3 - 16)</td>
<td>13 (6 - 19)</td>
</tr>
<tr>
<td>Age at onset of first anti-TNF (years)</td>
<td>10 (3 - 16)</td>
<td>11 (3 - 19)</td>
</tr>
<tr>
<td>Duration of uveitis (years)</td>
<td>4 (-4 - 13)</td>
<td>9 (3 - 15)</td>
</tr>
<tr>
<td>Interval: onset of JIA - uveitis (years)</td>
<td>3 (-4 - 15)</td>
<td>1.2 (-4 - 12)</td>
</tr>
<tr>
<td>Uveitis before arthritis</td>
<td>7 (16)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>0.91 (0.2–1.0)</td>
<td>0.96 (0.7–1.0)</td>
</tr>
<tr>
<td>Cystoid macular edema</td>
<td>5 (11)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Cataract</td>
<td>18 (40)</td>
<td>25 (56)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>6 (13)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Band keratopathy</td>
<td>5 (11)</td>
<td>8 (40)</td>
</tr>
</tbody>
</table>

5.2.2 Ophthalmologic characteristics and complications (II, III)

Between infliximab and etanercept treatment groups, no significant differences in ocular complications or visual acuity existed at baseline, despite glaucoma in 6 patients starting infliximab vs. in 0 of those starting etanercept (p=0.007). JIA onset occurred earlier in those on etanercept (mean 2 years, range 1-6) than in those on infliximab (mean 4 years, range 1-9, p=0.016). In baseline characteristics (Table 7), no other differences were observed. During two-year anti-TNF therapy, however, the frequency of ocular complications increased. One patient taking etanercept had sight-threatening macular edema and another had retinal ablation (II).

At adalimumab initiation 10 patients had complicated uveitis (Table 7). Ten had undergone ocular surgery before and three during follow-up, one of whom had an acute attack of ocular hypertension, hypopyon, and decrease in BCVA. Other ocular complications were also observed: in three eyes cataract and in one eye an increase of macular edema with decreasing BCVA (III).

5.2.3 Etanercept and infliximab in JIA-associated uveitis (II)

Inflammatory activity of uveitis improved more frequently in those taking infliximab than in those taking etanercept (Table 8). The number of AC cells decreased more often in the infliximab treatment group (p=0.047), as did also the number of uveitis flares/year (p=0.015).
We found no correlation between dose or frequency of infliximab infusions and ophthalmologic outcome. Of the 9 well-responding patients, the mean dose was 3.5 (range 2.8-4.7) mg/kg, and infusion intervals were 4 weeks in 2, 6 weeks in 4, 8 weeks in 2, and 10 weeks in 1 patient. Of the 4 patients with worsening AC activity, the mean dose was 3.2 (range 2.4-4.9) mg/kg, and infusion intervals were 4 weeks in 1 and 6 weeks in 3 patients. In the 8 patients with no change in AC activity, the mean dose was 3.5 (range 2.9-4.0) mg/kg, and infusion intervals were 6 weeks in 2 and 8 weeks in 6 patients (V).

Anti-TNF therapy was discontinued due to AEs in 2 patients taking etanercept (rash and recurrent skin infections in one and retinal ablation in the other) and in 4 patients taking infliximab (infusion reactions in 3 and an increase in DNA-Ab with alopecia in one). Discontinuation due to inefficacy occurred in 4 patients on etanercept and in 4 patients on infliximab, and due to inactive disease (arthritis and uveitis) in 2 patients on infliximab. The latter 2 patients remained in clinical remission on DMARDs for 5.2 and 0.5 years, respectively.

Severe AEs were observed in 4 patients taking etanercept (pneumonia, unspecified abdominal infection requiring hospitalization, sight-threatening macular edema, retinal ablation) and in 3 patients taking infliximab (peritonsillar abscess, pansinuitis, and alopecia with highly increased DNA-Ab). No life-threatening AEs were observed.

### 5.2.4 Adalimumab in JIA-associated uveitis (III)

Adalimumab was initiated due to uveitis in 5, active uveitis plus arthritis in 11, and arthritis in 4 patients. In 19 patients, the first-line biologics had started a mean of 38 months (range 16-67) earlier, and altogether 18 had taken infliximab prior to adalimumab. Based on SUN criteria, the activity of uveitis improved in 7 patients. The one whose activity worsened had active arthritis throughout the follow-up (Table 9).

Compared with nonresponders, those with improved activity were younger (11.0 vs. 14.7 years, p=0.046), had shorter duration of JIA (7.4 vs. 11.3 years, p=0.019), and a lower active joint count at baseline (1.7 vs. 4.9 joints, p=0.041), but not at the end of follow-up (0.7 vs. 2.6 joints, p=0.086). No differences in the use of DMARDs or corticosteroids were observed between responders and nonresponders. We found a negative association between

<table>
<thead>
<tr>
<th>Activity of uveitis</th>
<th>Etanercept n=24</th>
<th>Infliximab n=21</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened activity, n (%)</td>
<td>13 (54)</td>
<td>4 (19)</td>
<td>17 (38)</td>
</tr>
<tr>
<td>No change, n (%)</td>
<td>6 (25)</td>
<td>8 (38)</td>
<td>14 (31)</td>
</tr>
<tr>
<td>Improved activity, n (%)</td>
<td>5 (20)</td>
<td>9 (43)</td>
<td>14 (31)</td>
</tr>
<tr>
<td>Flares/year during therapy, n (range)</td>
<td>1.35 (0-3.2)</td>
<td>0.68 (0-2.0)</td>
<td>1.1 (0-3.2)</td>
</tr>
</tbody>
</table>
favorable outcome and duration of JIA (rs = -0.52, p=0.019), active joint count at baseline 
(rs = -0.534, p=0.015), and active joint count at follow-up (rs = -0.47, p=0.036), but not 
with the change in number of active joints.

Table 9
Activity of uveitis based on either SUN criteria (1) or modified criteria (2) during 
adalimumab therapy in 20 JIA patients with bilateral uveitis.

<table>
<thead>
<tr>
<th>Activity of uveitis on adalimumab</th>
<th>SUN criteria (1)</th>
<th>All eyes (1)</th>
<th>Modified criteria (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Improved activity, n (%)</td>
<td>7 (35)</td>
<td>8 (20)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>No change, n (%)</td>
<td>12 (60)</td>
<td>32 (77)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Worsened activity, n (%)</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

The mean number of uveitis flares/year decreased from 1.9 (range 0-12) before 
adalimumab to 1.4 (range 0-11.7) during adalimumab treatment. This decrease was 
insignificant (p=0.186) in all 20 patients, but closer to significance in patients with positive 
ANA (p=0.076) or negative HLA-B27 (p=0.084). The decrease was, however, significant 
in all 20 patients when variables were dichotomized with a cut-off point of one flare/year 
(p=0.039 in McNemar’s test), especially in those with positive ANA (p=0.016), but not in 
those with negative HLA-B27 (p=0.219). We observed neither significant associations nor 
predictors of the decrease in number of uveitis flares/year.

Altogether 7 of 20 patients discontinued adalimumab during follow-up, 6 because of 
infficacy (1 flare in uveitis, 1 flare in arthritis, 4 in both) and 1 because of subsiding 
uveitis and arthritis. In this patient, after 4 months arthritis was still in remission, but 
uveitis had relapsed (AC cells 1+/1+). Due to increased inflammatory activity, 4 patients 
were on weekly adalimumab dose of 40 mg without clear improvement in either uveitis or 
arthritis. Of these, 2 discontinued adalimumab due to inefficacy, 1 continued on a weekly 
dose, and 1 switched back to a standard dose because of recurrent respiratory infections. In 
one patient after the start of weekly adalimumab, uveitis became inactive.

Only 5 patients received oral prednisolone at the end of follow-up. Seven patients were 
able to discontinue prednisolone during adalimumab treatment, and 1 had to increase the 
dose. In all 20 patients, mean daily prednisolone intake decreased from 0.1 mg/kg (range 0-0.4) 
to 0.03 (range 0-0.3) mg/kg (p=0.057). Altogether 4 patients were able to switch from 
combination DMARDs to monotherapy, and in 3 of them the activity of uveitis and 
arthritis further decreased.

We observed no serious or life-threatening AEs. The calculated adalimumab exposure 
was 31 patient-years. Thirty infections (0.97 per patient-year) were recorded, most 
commonly upper respiratory infections. Two patients required oral antiretroviral treatment 
(varicella, recurrent herpes zoster), one antrostomy (recurrent sinusitis), and one 
gastroduodenoscopy (gastritis).
5.3 Impact of anti-TNF agents in arthritis (V, III)

5.3.1 Impact of etanercept and infliximab in arthritis (V)

Of the original cohort of 108 patients with JIA, altogether 45 had uveitis during etanercept and infliximab treatment. Of these 45 patients, at the end of 24-month follow-up or at the termination of anti-TNF therapy, 18/45 patients (40%) had inactive arthritis, and only 10/45 patients (20%) had clinical remission including quiescent uveitis (AC cells < 3). In 20/45 patients (43%) number of active joints, ESR and CRP had decreased by at least 70% but less than 100%, in 20 (43%) by at least 30% but less than 70%, and in 13 (29%) by less than 30%. Of these 13 patients with poor response to anti-TNF therapy in arthritis, uveitis improved in 3 and worsened in 6 patients. At baseline 63 patients without uveitis had more active joints compared with those with uveitis (Table 10). Disease activity parameters (CRP, ESR, number of active joints) were comparable during etanercept and infliximab treatment both at baseline and at the end of follow-up.

Table 10  Activity of arthritis and inflammation parameters, expressed as mean (range), at anti-TNF initiation (baseline) and at the end of follow-up. Cohort consists of 108 JIA patients, of whom 45 had also JIA-associated uveitis during anti-TNF treatment (V).

<table>
<thead>
<tr>
<th></th>
<th>Uveitis n = 45</th>
<th>Without Uveitis n = 63</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP at baseline (mg/l)</td>
<td>20 (5-63)</td>
<td>31 (5-159)</td>
<td>0.086</td>
</tr>
<tr>
<td>CRP at 24 months (mg/l)</td>
<td>8 (5-53)</td>
<td>13 (5-142)</td>
<td>ns</td>
</tr>
<tr>
<td>ESR at baseline (mm/hr)</td>
<td>32 (2-95)</td>
<td>36 (3-127)</td>
<td>ns</td>
</tr>
<tr>
<td>ESR at 24 months (mm/hr)</td>
<td>18 (2-98)</td>
<td>15 (2-99)</td>
<td>ns</td>
</tr>
<tr>
<td>Number of active joints at baseline</td>
<td>7 (0-36)</td>
<td>11 (2-47)</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of active joints at 24 months</td>
<td>2 (0-7)</td>
<td>2 (0-21)</td>
<td>ns</td>
</tr>
<tr>
<td>Oral prednisolone at baseline (mg daily)</td>
<td>0.2 (0-0.9)</td>
<td>0.2 (0-1.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Oral prednisolone at 24 months (mg daily)</td>
<td>0.1 (0-0.2)</td>
<td>0.1 (0-0.5)</td>
<td>ns</td>
</tr>
</tbody>
</table>

5.3.2 Efficacy of adalimumab in arthritis (III)

At the initiation of adalimumab therapy, 14/20 (70%) patients had active joints. At the end of follow-up for adalimumab, 6/14 patients (43%) had inactive arthritis and normal ESR and CRP. ACR Pedi30 response was observed in 57% at 6 months, in 60% at 12 months, and in 100% at 24 months (Figure 9). During adalimumab therapy, the decrease in number of active joints was significant (p=0.002), but not in ESR, CRP, CHAQ, or physician’s and parents’/patient’s VAS. Differences in outcome of arthritis were not explained by age, duration of JIA, type of JIA, ANA, HLA-B27, gender, number of DMARDs, corticosteroids, or onset of JIA.
Proportion of patients with clinical remission increased during adalimumab treatment. The number of patients with inactive disease increased from one patient at anti-TNF initiation to two patients at the end of follow-up if AC grade 0/0 was required for the definition of quiescent uveitis and clinical remission. However, the number of patients with clinical remission increased from 5 to 11 if that was defined as quiescent arthritis and quiescent uveitis with AC grade 0.5+/0.5+.104

5.4 Drug survival with anti-TNF agents (IV)

Long-term drug treatment survival was evaluated in 209 JIA patients receiving etanercept or infliximab as first-line anti-TNF therapy. For statistically meaningful comparisons, baseline characteristics of each treatment group were first evaluated. Compared with 105 patients taking etanercept, the 104 on infliximab had more frequently JIA-associated uveitis (29% vs. 43%, p=0.031), persistent oligoarthritis (1% vs. 14%, p=0.001), and ANA positivity (35% vs. 51%, p=0.024), less often sJIA (11% vs. 2%, p=0.019) or seronegative polyarthritis (p=0.013), and were older at JIA onset (4.5 vs. 5.6 years, p=0.023).

Baseline differences between genders occurred. Compared to females, males had less seronegative polyarthritis (8% vs. 42%, p<0.001), more ERA (10% vs. 0%, p<0.001), and fewer were ANA-positive (9% vs. 34%, p=0.022). Moreover, JIA onset in males occurred later (6.2 vs. 4.6 years, p=0.018) and its duration was shorter (4.2 vs. 5.4 years, p=0.007).

At baseline, the proportion of patients with high disease activity receiving etanercept and infliximab was 86% and 75%, respectively (p=0.155). The rest of the patients had moderate disease activity. Of the 209 patients, 205 (98%) received at least one DMARD;
27% were on single and 64% on combination therapy. Of the 205 patients, 166 were on MTX, 71 on hydroxychloroquine, 60 on CSA, 51 on sulfasalazine, 30 on azathioprine, and 137 on prednisolone (mean daily dose 8 mg or 0.3 mg/kg).

### 5.4.1 Drug survival with first-line anti-TNF agents

During 48-month follow-up, the proportion of patients continuing with etanercept or infliximab (Table 11) as the first anti-TNF therapy was comparable in nonadjusted model (p=0.194, Figure 10 A) as well as in gender- and disease activity adjusted models (p=0.092 and p=0.262, respectively). In this analysis, withdrawal from the anti-TNF agent due to an inactive disease was not considered as treatment discontinuation.

Drug survival with etanercept or infliximab according to JIA subtypes at 24 and 48 months was 92% and 92% in patients with oligoarthritis, 91% and 78% in ERA, 75% and 65% in extended oligoarthritis, 65% and 52% in seropositive polyarthritis, 62% and 47% in seronegative polyarthritis, and 54% and 24% in sJIA, respectively. In remaining subtypes, cases were too few for meaningful statistical comparisons. Drug survival between etanercept and infliximab was comparable in patients with seronegative polyarthritis (p=0.080), seropositive polyarthritis (p=0.578), ERA (p=0.548), and sJIA (p=0.433). Infliximab was discontinued more often in patients with extended oligoarthritis (p=0.019).

First-line anti-TNF therapy was discontinued in 43% of patients taking etanercept and in 59% of those taking infliximab: in 7 (7%) and 23 (22%) due to AEs, in 29 (28%) and 21 (20%) due to inefficacy, and in 10 (10%) and 17 (16%) due to inactive disease.

<table>
<thead>
<tr>
<th>Drug survival</th>
<th>Etanercept % (95% CI)</th>
<th>Infliximab % (95% CI)</th>
<th>Adalimumab % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>83 (76 - 90)</td>
<td>80 (72 - 87)</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>68 (59 - 78)</td>
<td>68 (58 - 77)</td>
<td></td>
</tr>
<tr>
<td>36 months</td>
<td>64 (54 - 74)</td>
<td>53 (42 - 64)</td>
<td></td>
</tr>
<tr>
<td>48 months</td>
<td>61 (50 - 71)</td>
<td>48 (36 - 59)</td>
<td></td>
</tr>
<tr>
<td>60 months</td>
<td>53 (41 - 65)</td>
<td>45 (33 - 57)</td>
<td></td>
</tr>
<tr>
<td><strong>Second-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>84 (70 - 98)</td>
<td>58 (39 - 76)</td>
<td>73 (51 - 96)</td>
</tr>
<tr>
<td>12 months</td>
<td>60 (41 - 79)</td>
<td>58 (39 - 76)</td>
<td>66 (42 - 90)</td>
</tr>
<tr>
<td>24 months</td>
<td>48 (26 - 70)</td>
<td>32 (14 - 50)</td>
<td></td>
</tr>
<tr>
<td>36 months</td>
<td>38 (14 - 65)</td>
<td>26 (7 - 44)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 10  Drug survival (%) with first-line anti-TNF agents etanercept or infliximab in JIA patients. Treatment discontinuation during a 48-month follow-up due to all reasons except inactive disease (A) and due to adverse events (B). Modified and reprinted with kind permission of Annals of Rheumatic Diseases (Tynjälä et al. In press).

Treatment discontinuation due to AEs, most commonly (93%) side-effects, occurred more frequently with infliximab than etanercept (Figure 10 B, p=0.002), also in the gender- and disease activity-adjusted models (p=0.001 and p=0.002). One patient on etanercept and one on infliximab discontinued the therapy due to fear of injections.

Treatment discontinuation due to inefficacy was comparable between etanercept and infliximab in nonadjusted (Figure 11 C, p=0.445), as well as in gender- and disease activity-adjusted models (p=0.600 and p=0.350).

Discontinuation rates due to inactive disease or remission seemed to be higher during infliximab than during etanercept therapy, but this difference was not significant in nonadjusted (Figure 11 D, p=0.068), gender-adjusted (p=0.059), or disease activity-adjusted (p=0.092) models.

Figure 11  Treatment discontinuation (%) due to inefficacy (C) or inactive disease (D) during a 48-month follow-up in JIA patients receiving etanercept or infliximab. Modified and reprinted with kind permission of Annals of Rheumatic Diseases (Tynjälä et al. In press).
Predictors of discontinuation of first-line agents

The risk for discontinuation due to AEs was higher in those taking infliximab rather than etanercept, and in girls compared with boys (Table 12). In addition, HLA-B27-positive patients had an 81% smaller risk of discontinuing anti-TNF agent due to AEs. When 64 males, 38 of which were on infliximab were analyzed independently from females, discontinuation rates due to AEs between infliximab and etanercept treatment groups were not different (p=0.638 in logrank test). The only predictor of anti-TNF discontinuation due to inactive disease was duration of JIA; a short duration of JIA at anti-TNF initiation predicted treatment discontinuation due to inactive disease or remission.

Infliximab was discontinued due to inactive disease in 17 patients receiving a mean dose of 3.6 (range 2.6-5.8) mg/kg and with a mean infusion interval of 9.3 (range 8-12) weeks. By contrast, 22 patients discontinued infliximab due to infusion reactions at a mean time of 9.6 (range 0.5-35) months from anti-TNF initiation; these patients received a mean dose of 3.1 (range 2.2-5.0) mg/kg and had a mean infusion interval of 6.2 (range 4-8) weeks. Compared with the 17 patients with inactive disease, these 22 patients received a similar dose (p=0.147), but had a shorter dose interval (p=0.001).

In 65 patients on infliximab as either first- or second-line therapy and without hypersensitivity reactions, the mean infusion interval was 7.3 (range 4-12) weeks with a mean dose of 3.9 (range 1.9-11.1) mg/kg. The difference between doses of patients with or without infusion reactions was 0.8 mg/kg [(95% CI 0.2 to 1.0), p=0.025]. No significant predictors of infusion reactions were found.

Table 12  Predictors of discontinuation based on Cox regression and hazard ratios (HRs) during first-line treatment with infliximab and etanercept in 209 JIA patients.

<table>
<thead>
<tr>
<th>Predictors of discontinuation</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to all reasons except inactive disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>2.8</td>
<td>1.3 - 5.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Systemic JIA</td>
<td>7.8</td>
<td>1.7 - 34.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Infliximab therapy</td>
<td>2.0</td>
<td>1.2 - 3.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Due to inefficacy only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic JIA</td>
<td>4.2</td>
<td>1.3 - 14.1</td>
<td>0.020</td>
</tr>
<tr>
<td>Seronegative polyarthritis</td>
<td>2.2</td>
<td>1.0 - 4.8</td>
<td>0.048</td>
</tr>
<tr>
<td>Due to AEs only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab therapy</td>
<td>4.6</td>
<td>1.8 - 11.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Negative HLA-B27</td>
<td>5.2</td>
<td>1.5 - 18.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Female gender</td>
<td>5.4</td>
<td>1.1 - 26.9</td>
<td>0.039</td>
</tr>
<tr>
<td>Due to inactive disease only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of JIA</td>
<td>0.77</td>
<td>0.64 - 0.94</td>
<td>0.008</td>
</tr>
</tbody>
</table>
5.4.2 Switch to second-line anti-TNF agents

Altogether 73 patients (35%) switched biologic therapy: the majority, 77%, from etanercept to infliximab or vice versa, 20% to adalimumab, and 3% to anakinra. Mean treatment time was 18 months (95% CI 14 to 22) during the first and 16 months (95% CI 13 to 20) during the second course of therapy (p=ns). The proportion of females was higher (p<0.001) among those who switched therapies (88% of 73) than in nonswitchers (60% of 136). Drug treatment survival with etanercept, infliximab, or adalimumab as the second biologic agent (Table 12) was comparable (p=0.196 in logrank test, Figure 12). In the switchers, the discontinuation rate due to AEs or inefficacy during first-line anti-TNFs was 96% and during second-line biologics 53%, significantly less frequent in McNemar’s test (p=0.001).
Predictors of discontinuation of second-line agents

The second biologic agent was discontinued in 39 patients (53%): in 13 patients due to AEs, in 26 patients due to inefficacy, and in 4 patients due to inactive disease. Systemic JIA increased the risk for discontinuation also during second-line anti-TNF therapy (Table 13).

Table 13 Predictors of discontinuation based on a Cox regression model and hazard ratios (HRs) during second-line biologic treatment with etanercept, infliximab, adalimumab, or anakinra in 73 JIA patients.

<table>
<thead>
<tr>
<th>Predictors for discontinuation</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to both inefficacy and AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic JIA</td>
<td>4.5</td>
<td>1.8 - 11.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Failure of first course with etanercept</td>
<td>2.2</td>
<td>1.4 - 4.2</td>
<td>0.019</td>
</tr>
<tr>
<td>Due to inefficacy only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic JIA</td>
<td>9.4</td>
<td>3.1 - 28.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative ANA</td>
<td>2.8</td>
<td>1.2 - 6.5</td>
<td>0.019</td>
</tr>
<tr>
<td>Due to AEs only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure of first course with etanercept</td>
<td>12.6</td>
<td>2.5 - 64.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Discontinuation of first course due to AEs</td>
<td>6.8</td>
<td>1.6 - 28.7</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Restart or switch to third-line agents (V)

In 15% of 209 patients, the first anti-TNF treatment was restarted after a disease flare following earlier treatment discontinuation. Restarted therapy was considered successful if patients continued it during follow-up. The success rate was similar in etanercept and infliximab: 9/19 (47%) and 8/12 (67%), respectively (p=0.120).

After failure with the second biologic agent, 13 patients from the original etanercept group and 7 patients from the original infliximab group switched to third-line biologic agent. Switch was successful in 6/13 patients (46%) and in 2/7 patients (29%), respectively, when the mean follow-up period was 8 (range 1-21) months, exceeding one year only in 6 patients (V).
6 DISCUSSION

During the last decade, TNF modulators have provided a major step forward in the treatment of rheumatic disorders. In researcher-initiated studies, the focus has been on the evaluation of long-term safety and efficacy in real-life settings. Such studies are important with regard to new medicinal preparations and vulnerable patient groups, e.g. children with JIA receiving biologic agents. In the present study, attention was directed to long-term evaluation of anti-TNF therapies, including analyses of growth, activity of uveitis, ocular complications, and treatment survival.

6.1 Growth during anti-TNF treatment (I)

6.1.1. Changes in growth velocity

The analysis of growth in 71 patients with JIA demonstrated a favorable treatment effect for etanercept and infliximab. Patients whose growth velocity had slowed down showed significant improvement after the initiation of anti-TNF treatment. The potential for catch-up growth was highest in those with the greatest growth retardation, and the growth rate prior to anti-TNF therapy was the strongest predictor of the quantity of change. The effects of etanercept and infliximab on growth were comparable. A decelerating growth velocity throughout the four-year follow-up was associated with a higher glucocorticoid dose, older age at anti-TNF onset, and poorer response to anti-TNF therapy. We suggest that the finding of improved growth velocity during anti-TNF therapy is due to decreased inflammation and cytokine levels. In JIA, increases in pro-inflammatory cytokines TNFα, IL-1β, and IL-6 may have both local and systemic effects on growth, and their expression is known to be associated with increased inflammatory activity. In animal models, Martensson et al. showed that TNFα locally suppressed longitudinal bone growth, which was only partially reversed by IGF-1. Although the precise etiology of the growth retardation in JIA is unknown, pro-inflammatory cytokines have been proposed to be directly associated with growth failure. In a recent study, in vitro neutralization of IGF-1 and pro-inflammatory cytokines by specific antibodies did not improve metatarsal growth. The observation suggests that factors other than pro-inflammatory cytokines may have an effect on growth, possibly through IGF-1 independent mechanisms. Among clinical studies, both our investigation and two other reports have demonstrated that anti-TNF therapies are effective in suppressing inflammation and restoring growth velocity. In the latter two studies, JIA patients received etanercept, whereas in our series patients received both etanercept and infliximab. Schmeling et al. observed improved linear growth in 7 children with previous growth delay, and more recently Vojvodich et al. reported growth improvement in 81% of 31 JIA patients receiving etanercept. Our results are in line with these studies.
The effect of anti-TNF therapy on skeletal maturation remains obscure. The present results suggest that a pathological acceleration in skeletal maturation is unlikely, i.e. no abnormal advance in bone age was observed.

During the use of anti-TNF agents, BMI increased excessively in 10% of subjects. The exact reason for this is unknown, and to our knowledge, no previous studies in children have reported such an increase during treatment with anti-TNF agents. TNFα has been suggested to be involved in body weight homeostasis, which may therefore be affected by TNFα targeted therapy. During the course of rheumatic diseases and different treatment strategies, obesity and lipid metabolism remain intriguing research subjects, which have seldom been explored in children. As a functional precaution to avoid obesity, JIA patients achieving inactive disease should be encouraged to exercise at least as much as their healthy peers.

6.1.2. Impact of corticosteroids and treatment response on growth

One reason for growth retardation in JIA is corticosteroids. The present results are consistent with this finding. We observed that the four-year cumulative dose of oral glucocorticoids and intra-articular steroids was an independent variable predicting the change in growth velocity during the follow-up. The intake of steroids was directly associated with more severe growth disturbance. Yet, in the multivariate regression model, glucocorticoids merely had a moderate effect, suggesting that their impact was only one of many affecting growth. Glucocorticoids are known to disturb longitudinal growth through several mechanisms, by directly affecting the growth plate and interfering with the GH/IGF-1 axis, among others. Based on the present results, anti-TNF therapies resulted in decreased glucocorticoid intake, thus minimizing steroid-related side-effects.

However, it must be noted that all patients did not benefit from anti-TNF therapies. Of the 71 patients, 7% were nonresponsive, with improvement of less than 30% in at least one of the three disease activity measures (ESR, CRP, number of active joints). In addition, poor response to anti-TNF therapy was associated with delayed growth also after anti-TNF onset. Although growth velocity increased after initiation of anti-TNF therapy in the majority of patients, midparental target height was not achieved during the follow-up. Long-term corticosteroid therapy has been shown to reduce final height, and 30% of patients have no catch-up growth following disease remission.

6.2 Activity of uveitis during anti-TNF treatment

6.2.1 Etanercept and infliximab (II)

The cohort we followed consisted of 108 JIA patients commencing biologic treatment in 1999-2001. All patients were refractory to conventional treatment with DMARDs. The
first-line anti-TNF agent was typically initiated due to arthritis, and only in 5% due to uveitis. This is partly because of previous and present administration of anti-TNF agents in uveitis being off-label. Interestingly, the occurrence of uveitis in our refractory JIA cohort was 44%, which is much higher than the 20% described in most earlier series.13 Almost two-thirds of our patients had seronegative polyarthritis, in which the occurrence of uveitis is usually 5-24%.10, 42, 120, 121 During the two-year follow-up, the frequency of long-term complications of uveitis seemed to increase despite decreased ocular inflammatory activity. This reflects the chronicity and inevitable long-term consequences of childhood uveitis regardless of adherence to current treatment. At the initiation of anti-TNF therapy in our cohort, uveitis had already persisted for five years in 38% of patients, and for more than a decade in 11%.

The optimal treatment for uveitis is not thoroughly known. Early detection and effective treatment form the basis for a better prognosis.12, 123, 124 Early initiation of immunomodulators is recommended to avoid the sight-threatening complications of uveitis and the side-effects of topical and oral steroids. The most frequently initiated conventional immunomodulator, MTX, has been suggested to be effective or even to induce remission.122, 186, 188 Less reports exist on the potential benefits of CSA.170, 189 The increasing use of anti-TNF therapy in rheumatic diseases has led to studies of the effect of biological drugs on uveitis.

Although studies on uveitis in JIA patients are few and observational, they have been rather consistent regarding the effects of etanercept and infliximab. Etanercept has been suggested to have minor or no effect on uveitis even in one small RCT,249, 250 whereas only positive reports on the efficacy of infliximab have been published.253-256 To date, one questionnaire-based survey has reported the outcome of etanercept and infliximab treatment in JIA-associated uveitis.260 In other retrospective and smaller patient series, the study population has been even more heterogeneous, consisting of patients with sarcoidosis, Beçhet disease, JIA, ankylosing spondylitis, RA, or adults with other conditions.

To our knowledge, the present uveitis series, with 45 JIA patients and a follow-up of up to two years, is in children the largest published report on etanercept and infliximab treatment in JIA-associated uveitis. Our retrospective analysis suggests that anti-TNF therapies have beneficial effects in JIA patients with uveitis. Infliximab, a monoclonal TNFα antibody, seemed to demonstrate a more favorable effect than etanercept, a soluble TNF receptor, in controlling ocular inflammation.

### 6.2.2 Adalimumab (III)

During adalimumab therapy, uveitis improved in 35% of patients. Patients with a favorable response were younger, had a shorter duration of JIA, and had a lower active joint count at baseline. Of note, 95% of the 21 JIA patients in this series had an insufficient response to previous second-line agents combined with first-line anti-TNF therapy, indicating that this series represented those with a refractory course of uveitis. Based on published reports, adalimumab has demonstrated an acceptable safety profile, a low rate of serious AEs, and
none of the hypersensitivity reactions found with infliximab.\textsuperscript{234, 235, 257, 258} Adalimumab, thus, is an interesting treatment option in refractory uveitis.

Although one-third of patients with refractory uveitis improved, we did not observe as beneficial an ophthalmologic outcome as reported in the three investigations described below. Biester \textit{et al}.\textsuperscript{257} documented improvement in 89\% of patients, but favorable response was based on number of relapses. However, their patients had a shorter duration of disease than in our series. Vazquez-Cobian \textit{et al}.\textsuperscript{258} showed improved activity in 81\% of eyes, which is markedly more than the 20\% in our series. Their patients were younger, the underlying conditions were different, and the definition of improvement was not as stringent as in our series. A recent survey lacking detailed ophthalmologic data reported that all three patients who had experienced failure with infliximab had a favorable response to adalimumab.\textsuperscript{260} Compared with earlier results, differences in patient characteristics and response criteria in our study may explain the lower rate of favorable outcome.

The majority (90\%) of our patients were considered infliximab failures because of either inefficacy or side-effects. This is clearly different from the series of Biester \textit{et al}.\textsuperscript{257} where only 28\% had experienced failure with infliximab. Infliximab doses of 3-5 mg/kg, recommended in the early years, are probably suboptimal for the treatment of uveitis. In a recent publication, patients with refractory uveitis were treated successfully with infliximab doses of up to 10-20 mg/kg.\textsuperscript{256} However, no toxicity analyses of high-dose infliximab treatment have yet been published, and the high costs of this treatment may limit its further use.

When evaluating the AC cell activity in uveitis, we tested both the recently published SUN criteria\textsuperscript{107} and modified criteria.\textsuperscript{268, 269} The results between these two methods did not differ appreciably, although the proportion of patients without any change in the activity of uveitis was higher when assessed by SUN criteria, which is due to the requirement of a two-step change in the activity of uveitis. This requirement may diminish the confounding effect of spontaneous fluctuation in the number of AC cells on the results. To facilitate the comparison of different studies in the future, a consensus on common response criteria is needed.

\textbf{6.2.3 Impact of anti-TNF agents in uveitis (II-III)}

Anti-TNF drugs offer an exciting treatment option for refractory uveitis, but their mechanism of action in the eye is not fully understood, and the efficacy of monoclonal TNFα antibodies has not yet been proven by any RCT. It may be speculated that the clinical perception of better efficacy of TNFα antibodies in uveitis in JIA could be explained at least partly by different binding characteristics. Whereas soluble TNF receptor etanercept binds primarily to soluble TNF, both infliximab and adalimumab bind to soluble and membrane-bound TNFα. Infliximab is also capable of deleting T-cells producing TNFα. Differences in binding may lead to differing effects on complement activation and apoptosis, which may in turn have an impact on uveitis.

Another observation based on the present results is the high rate of complications. In patients receiving adalimumab, the mean duration of uveitis was nine years. Although
BCVA was not decreased at the end of the follow-up, up to 70% of patients had cataract, 55% glaucoma, 40% band keratopathy, and 40% macular edema, when anti-TNF agents had been initiated only for a mean of two years earlier. The high rate of complications, despite of ongoing second-line and third-line therapy, underlines the importance of early effective treatment of anterior uveitis.

6.3 Anti-TNF agents in arthritis (III)

6.3.1 Etanercept and infliximab (V)

In JIA, an impressive efficacy of etanercept and infliximab has been demonstrated in a few prospective trials; in etanercept, a sustained efficacy has been shown for up to 8 years, and in infliximab, an efficacy for up to one year. In the present study, we reported changes in disease activity parameters, i.e. ESR, CRP, and active joint count. Due to the retrospective setting and nonrandomized treatment groups, we were unable to perform full efficacy analysis or to compare the efficacy of etanercept and infliximab treatment. However, the impact of etanercept and infliximab in our series, especially in patients with elevated active joint count at baseline, was in line with that of prospective RCTs or open-label studies, with a markedly decreased active joint count at the end of follow-up and no apparent differences between etanercept and infliximab treatment groups (V).

6.3.2 Efficacy of adalimumab (III)

In RA, long-term data on adalimumab have demonstrated sustained efficacy and an acceptable safety profile, both efficacy and safety being comparable with other TNF antagonists. No prospective studies on the efficacy of adalimumab in JIA patients have yet been published. The findings of a two-year efficacy trial in JIA were recently reported as an abstract, where the ACR Pedi30, 50, and 70 responses were 94%, 93%, and 81%, respectively. Our study sample was much smaller, the median duration of JIA was 12 years at the onset of adalimumab, and the long-term response rate was considerably lower than in the series of Lovell et al. In the retrospective series of Biester et al., adalimumab induced inactive arthritis in 63% of patients, and our findings were more in line with this series. The prospective multicenter RCT of Lovell et al. consisted of selected patient series, whereas the patient cohort in our series represented a real-life clinical series. This may at least partly explain the different response rates between the studies.

In this series, in the majority of patients, the favorable responses to arthritis and uveitis seemed to run different courses. Thus, optimizing a treatment of a child who has at times flares in arthritis or in uveitis is remarkably challenging, and requires close collaboration of pediatric rheumatologists and ophthalmologists.
6.4 Drug survival with anti-TNF agents (IV)

6.4.1 Drug survival and switch

In a real-life setting, the four-year treatment survival with anti-TNF agents etanercept and infliximab in JIA was comparable. During infliximab therapy, however, the discontinuation rate due to AEs, but not due to inefficacy or inactive disease, was higher than during etanercept therapy. Although our patient series reflected the heterogeneous population of clinical practice, the drug survival rate of first anti-TNF therapy was in line with that seen in prospective efficacy studies on etanercept and infliximab. Compared with the prospective series of Ruperto et al., treatment discontinuation due to AEs with infliximab in our patient series occurred more often and earlier. Throughout 1999-2004, we used the recommended 3 mg/kg doses, which are now known to be associated with infusion reactions more frequently than 6 mg/kg doses. This may at least partly explain the difference in discontinuation rates. Also the development of anti-TNF drug-specific antibodies has been observed, and may partly explain the weaning of therapeutic effect.

To the best of our knowledge, our study is the first in JIA to evaluate switching between anti-TNF therapies. Of patients discontinuing the first anti-TNF agent, approximately half were able to continue the second throughout the four-year follow-up. In a UK register study, 73% of RA patients switching biologic agents continued the second anti-TNF agent for a mean of six months, which is consistent with our findings. Although AEs in our study were different from those in the UK series, discontinuation of the first anti-TNF agent due to AEs was related to discontinuation of the second agent due to AEs in both series. Inefficacy of the first anti-TNF agent did not seem to predict inefficacy of the second anti-TNF agent in JIA, while in RA discontinuation rates due to inefficacy during the first and second course of anti-TNFs were associated. This suggests that in JIA switching from one anti-TNF agent to another can be considered a reasonable therapeutic option. However, analysis of larger series in those JIA patients switching biologic agents is still needed.

In adults, some preliminary evidence has been reported on the benefits of early aggressive anti-TNF treatment to induce remission. In the BeSt study, the combination of initial infliximab and MTX led to a higher remission rate and more often discontinuation of all anti-rheumatic drugs than conventional treatment strategies. Interestingly, in our study, commencement of anti-TNF treatment early in the course of JIA was associated with discontinuation of anti-TNFs due to inactive disease, which suggests indirectly that early anti-TNF treatment may induce clinical remission.

6.4.2 Patient outcome in JIA subtypes and subgroups

Baseline characteristics of those receiving etanercept and infliximab as a first-line TNF blocker were markedly different. Pediatric rheumatologists seemed to initiate infliximab more often to somewhat older children and to those with uveitis. By contrast, almost all
patients with sJIA received etanercept. Several explanations for this selection bias are possible. First of all, the limited supply of etanercept at the beginning of this millennium led in Finland to off-label pediatric use of infliximab for several years before the publication of the first RCT in JIA.\textsuperscript{223} Without any pediatric safety and toxicity studies available, infliximab was administered off-label, preferably to older children. Moreover, based on initial clinical observations, infliximab and adalimumab have been preferred in JIA patients with refractory uveitis, although no randomized studies have confirmed the better efficacy of monoclonal TNF\textsubscript{a} antibodies in uveitis compared with etanercept.

Of the JIA subtypes, treatment termination due to inefficacy during both the first and the second anti-TNF therapies was strongly associated with systemic onset JIA. This is hardly surprising because the response of biologic therapy in JIA seems to be subtype-specific.\textsuperscript{225, 228} In sJIA, a few studies have investigated the efficacy of etanercept, but little is known about the efficacy of other anti-TNF agents. Kimura \textit{et al.}\textsuperscript{276} reported that of their 45 sJIA patients more than 50\% had a poor or fair response to etanercept. Other studies have reported discontinuation rates of etanercept of up to 42\%.\textsuperscript{225, 228} In our cohort, this was even higher; during the first course of anti-TNFs, the discontinuation rate in patients with sJIA was 69\% and during the second course 100\%. In our study, a few patients receiving IL-1 receptor antagonist anakinra as a second-line biologic agent were observed to have poor treatment survival. In sJIA, some promising results on the efficacy of anakinra treatment exist,\textsuperscript{237} although the efficacy in juvenile patients is probably not as good as in adults.\textsuperscript{31}

In patients with ERA, 56\% of whom were HLA-B27-positive, the discontinuation rate was quite low, only 14\%. This concurs with previous findings of 19\% in 26 patients with ERA in the German etanercept registry,\textsuperscript{228} with sustained efficacy of etanercept of over two years in 8 ERA patients (7 HLA-B27-positive) in the study of Henrickson and Reiff,\textsuperscript{229} and with sustained efficacy of anti-TNF therapy of over one year in 10 HLA-B27-positive patients with JSPA.\textsuperscript{230} In our cohort, HLA-B27 positivity and male gender, but not ERA, were protective factors against treatment discontinuation due to AEs. This may in part be explained by the higher proportion of females among the poorer-responding and HLA-B27-negative patients with sJIA or highly active polyarthritis, but may also be an independent factor, thus warranting further investigation. In RA patients receiving biologic agents, females are less likely to achieve remission.\textsuperscript{275} In JIA, female gender has been demonstrated to be a predictor of disability\textsuperscript{61} and continued disease activity.\textsuperscript{57}

\textbf{6.5 Limitations of the study (I-IV)}

Our series represent a real-life cohort of anti-TNF users, with the limitations being those of many retrospective and register studies. However, all patients starting anti-TNF therapy were included. Moreover, due to continuous disease activity in these refractory patients, none was lost to follow-up, and long-term treatment took place regularly in the same tertiary pediatric rheumatology clinics. In this way, we were able to collect a large amount of information on a rare patient group.
In the study of growth (I), neither pubertal staging nor target height was assessed for all patients. Instead, to estimate the timing of the pubertal growth spurt, we used bone age measurements. Although our study was retrospective, this made analysis of growth more precise.

In the studies on uveitis, at least during 1999-2001, improvement of uveitis during infliximab therapy was not yet widely recognized. Thus, in the early years of anti-TNF treatment, selection bias can be considered quite low (II) compared with the later phases of the study (III). However, in our first study on uveitis (II), patients were not randomized into treatment groups, and the conventional therapy for all patients was also not similar. In the future, RCTs will be needed to reveal whether a true clinically and statistically significant difference exists between the treatments. Additionally, when we started our data collection, no international consensus on the improvement criteria of uveitis existed. Only after submitting our first manuscript on uveitis (II) were the SUN criteria published. In our second study of uveitis, we therefore evaluated the results with two methods (III).

In our patient series, the high proportion of patients receiving monoclonal TNFα antibodies with JIA-associated uveitis may have affected drug survival and discontinuation rates (IV). Moreover, due to the retrospective setting, the six core measures of the ACR Pediatric criteria were unavailable for all patients, and thus, we were unable to perform a complete efficacy analysis (IV, V).
7 CONCLUSIONS

In JIA, normal growth and development are essential aims of treatment, which cannot be achieved without a good control of disease activity. Growth retardation and reduced final height are among the disabling complications of especially polyarticular and systemic JIA. For these patients, the recently introduced anti-TNF therapies and other biologic disease modifiers are the most promising treatment options available. In most cases, combined with conventional therapy, biologic agents can sufficiently control refractory rheumatic inflammation and minimize steroid-related side-effects. Thus, the goal of current treatment strategy, remission, may be reached. Patients with inactive disease are the most likely to avoid the long-term consequences of JIA.

For JIA-associated anterior uveitis, no optimal therapy exists at the moment. In non-responsive cases, treatment should be intensified with early immunosuppressive drugs, which fail to control AC inflammation of the eye in 20% of patients. The longer the disease is uncontrolled, the poorer the outcome will be. Although we still lack more specific therapy, both in vitro and in vivo studies with anti-TNF agents and other biologic therapies provide a promising approach in uveitis. Unfortunately, the optimal timing of second- and third-line therapy with conventional and/or anti-TNF agents is not yet well known.

In our JIA series (I), anti-TNF therapy with etanercept or infliximab was highly effective in controlling the rheumatic inflammation. In most children refractory to conventional disease-modifying drugs and with compromised growth, anti-TNF agents were effective in restoring normal growth and even in inducing catch-up growth. The more growth velocity had been impaired, the higher was the potential to catch-up growth. Reduced inflammation was one of multiple factors positively affecting growth, as was also reduced intake of corticosteroids.

In our retrospective case series (II, III), JIA-associated uveitis improved in one-third of patients receiving anti-TNF agents. Treatment especially with monoclonal TNFα antibodies infliximab and adalimumab seemed to be profitable, whereas treatment with the soluble TNF receptor etanercept was less beneficial. Our current sequence of treatment in refractory uveitis is MTX combined with topical steroids and in non-responsive cases, infliximab. The present results suggest that adalimumab may be an equivalent treatment option to infliximab, and may be useful even in infliximab failures. However, prospective randomized studies will be needed to evaluate efficacy and safety of biological drugs in JIA-associated uveitis in a stringent scientific fashion.

Results of the long-term monitoring of JIA patients suggested that the overall treatment survival of etanercept and infliximab as the first-line biologics was comparable (IV), although infliximab was discontinued more often due to AEs. Among the subtypes of JIA, risk for treatment discontinuation was highest in systemic arthritis. Female gender was an independent risk factor for treatment discontinuation. Even as second-line anti-TNF agents, treatment survival with etanercept, infliximab, or adalimumab was satisfactory. Thus, a switch to another anti-TNF agent for non-systemic JIA patients who experience failure with the first anti-TNF agent can be recommended. In the future, other biologic compounds may provide therapeutic options for JIA patients refractory to anti-TNF agents.
8 REFERENCES


