Effects of Sulfasalazine Treatment in Juvenile Idiopathic Arthritis: Clinical and Radiological Observations

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Aan mijn ouders
Voor Pomme en Ger

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an umbrella term referring to a group of disorders characterized by chronic idiopathic inflammation of one or more joints (1). JIA is the most common chronic rheumatic illness in children and is a significant cause of short- and long-term disability. JIA is a clinical diagnosis, which is made in children less than 16 years of age with arthritis (defined as swelling or limitation of motion of the joints accompanied by pain or tenderness) of at least 6 weeks duration and with no other apparent cause. There is no pathognomonic test for JIA; it remains a diagnosis of exclusion.

The frequency of occurrence is not precisely known. Based on European studies, the incidence is estimated between 5 and 22 per 100.000 children per year (1 per 10.000), and the prevalence is 20 to 150 per 100.000 children (1 per 1000) (2-5). In the Netherlands, between 3000 and 4000 children have a diagnosis of JIA with a yearly increase of approximately 300 newly diagnosed patients.

There is no cure for JIA; the majority of children has continuing or recurrent disease that often extends into adulthood (6-10). JIA can lead to destructive lesions of cartilage and periarticular bone. Radiographs can document this damage and are used widely by clinicians to assess disease severity and progression. The extent of radiological damage varies with the type of JIA and the definition of radiological damage (11).

1. Nomenclature and classification of juvenile arthritis

Three separate systems of diagnostic and classification criteria have been used to classify patients under 16 years with chronic arthritis: the American College of Rheumatology (ACR, formerly American Rheumatism Association – ARA), the European league Against Rheumatism (EULAR), and the International League of Associations for Rheumatology (ILAR) classification system (1,12-14). In all three systems, a classifying diagnosis of patients' chronic arthritis is made when the specific criteria are fulfilled. Differences in criteria and nomenclature should lead to caution when interpreting the literature on juvenile arthritis.

In North America, the preferred term since the 1940's has been juvenile rheumatoid arthritis (JRA) as defined by the ACR (12). The ACR classification criteria describe 3 principal subtypes of JRA based on clinical features during the first 6 months of disease: pauciarticular or oligoarticular (with arthritis in < 5 joints), polyarticular (with arthritis in ≥ 5 joints) and systemic (with fever, rash, or other systemic manifestations). These criteria, however, do not account for children with spondylarthropathy or psoriatic arthritis (15).

In Europe, the term juvenile chronic arthritis (JCA) as defined by EULAR was preferred (13). This classification system contains similar onset types as described by the ACR criteria (pauciarticular or oligoarticular, polyarticular and systemic), but the classification is based on clinical symptoms during the first 3 months of disease. In addition, JCA includes the spondylarthritides and psoriatic arthritis, although it does not distinguish between the latter two groups. Later, additional classification criteria were proposed for juvenile

spondylarthropathy (16-18) and psoriatic arthritis (often referred to as 'Vancouver criteria') (19).

In order to overcome limitations of the earlier classification systems and to facilitate research, the ILAR proposed (20), revised (21) and further revised (1) criteria for JIA. In the ILAR classification system 6 diagnostic categories are defined using specific inclusion and exclusion criteria in an effort to maintain homogeneity within each category and to avoid overlap. A seventh 'undifferentiated' or 'other' category is included for patients that do not fulfill criteria for any other category, or fit in more than one category. The classification criteria for JRA, JCA and JIA, including the definitions of the subtypes of JIA are summarized in Table 1. According to the JIA definition, patients are classified 6 months after disease onset based on clinical symptoms, laboratory results and family history. The JIA classification is not an 'end point' diagnosis but a 'time point' diagnosis. It requires a regular update as other symptoms may evolve during the disease course.

In the early nineties, when we started the first study presented in this thesis, patients were recruited according to the EULAR criteria. The study and its results are described with the use of the terms oligoarticular, polyarticular and systemic JCA. Later, when the ILAR criteria were defined, we reclassified our study patients according to these criteria, and in the follow-up study we use the JIA classification. In the introduction and discussion of this thesis, the term 'juvenile idiopathic arthritis' (JIA) is preferred except when referring to specific citations.

2. Etiology and pathophysiology of juvenile idiopathic arthritis (JIA)

The etiology of JIA remains elusive. Two observations are paramount in considering etiology and pathogenesis (22-24). First, JIA is considered to be an *autoimmune disease* with evidence of dysregulation of the innate and adaptive immune response. The inflamed synovium of children with JIA suggests a cell-mediated pathogenesis as it shows a dense infiltration of T lymphocytes. T-cells are also the predominant mononuclear cells in the synovial fluid (25,26). In most instances, the T-cells from the synovial fluid and tissue have increased expression of activation markers (25-28). There is an imbalance detectable between pro- and anti-inflammatory cytokines in body fluids and synovial tissue, with an excess of pro-inflammatory cytokines (e.g. IL-1, IL-6, TNF) in active disease (29,30). Serum immunoglobulin levels tend to be elevated in active JIA. The presence of multiple autoantibodies in serum of JIA patients, such as anti-nuclear antibodies (ANA), rheumatoid factor (RF) and antibodies against citrullinated proteins (anti-CCP) indicate potential humoral abnormalities (22,24,31-33). Antibodies to citrullinated proteins are currently used as a novel and more specific test that can aid in the diagnosis of adult rheumatoid arthritis (RA) and in the determination of disease prognosis (34-42).

Second, JIA is considered a *complex genetic trait* that involves the effects of multiple genes related to immunity and inflammation (43). Major histocompatibility complex (MHC)

-associated risk factors within different subtypes of JIA have been demonstrated in numerous series (44,45). HLA-B27 was the first HLA association to be demonstrated with JIA, i.e. the current JIA subtype enthesitis related arthritis (ERA) (46). The MHC Class I antigen HLA-A2, in combination with specific MHC Class II genes, is associated with early onset oligoarthritis in girls (45,47). The MHC Class II genes, HLA-DR1 and HLA-DR4 have been associated with polyarticular JIA (23,45). HLA-DR4 (DRB1*0401) has a strong association with IgM rheumatoid factor positive JIA, supporting the theory that this represents the same disease as in adult RA. MHC coded non-HLA polymorphisms have also been associated with JIA (48,49); genes conferring risk include cytokine production-regulating genes (50,51). Data using genome wide scanning techniques in affected sib-pair families provide further evidence that multiple genes influence susceptibility to JIA (52,53).

According to current insights, it is hypothesized that development of JIA may be triggered by interference with environmental factors in a genetically predisposed child, at a point of vulnerability defined by age, intercurrent illness, prior antigenic experience, and immunologic maturity. Whether JIA is principally an immunogenetically determined disorder or an antigen-driven immunologic response is uncertain and may be different among the subtypes (54).

3. Therapy of JIA until the early nineties

Until the nineties, treatment in JIA was empirical and based on open studies and anecdotal reports. The central paradigm concerning JIA that governed therapy and thinking was "80% of children with JRA can expect to be rid of inflammation when they reach adulthood" and "80% of the children with JRA will grow up without deformity" (55). Many parents interpreted these statements as implying that something magical or important would happen at puberty to resolve their child's arthritis. These assumptions were based on studies that showed a good outcome in most young adult JIA patients (56,57). The treatment of JIA was often thought of as a pyramid with the base formed by non-steroidal anti-inflammatory drugs (NSAIDs), patient and family education, physical therapy, occupational therapy, and family support. Disease-modifying antirheumatic drugs (DMARDs) were usually added to this base in a slow step-wise fashion as the disease persisted longer and longer.

The rationale for using DMARDs was based on their efficacy in the adult rheumatic diseases. Later, when Wilske and Healy presented an aggressive treatment plan for RA based on treatment with multiple medications at the time of diagnosis, and then a gradual discontinuation of medications as (and if) patients improved, referred to as 'inverting the pyramid', concepts for JIA treatment were also challenged (58). In an article entitled "Dismantling the pyramid" Levinson and Wallace proposed a reassessment of conventional JIA treatment based on a critical evaluation of outcome studies that showed a dismal long-term outcome in a significant proportion of patients (6,55). At that time, only a few placebo-controlled studies in JIA had been performed. These studies had shown disappointing efficacy of commonly used DMARDs in JIA: D-penicillamine, hydroxychloroquine (59), and

oral gold (60). Some open studies in JIA had shown promising results of treatment with two other DMARDS: methotrexate (61-65) and sulfasalazine (66-71).

In this timeframe, the Dutch Juvenile Chronic Arthritis Study group initiated the first randomized placebo-controlled trial with sulfasalazine as the study drug (72). This study is presented in **Chapter 2.**

4. Sulfazalazine therapy in rheumatic diseases

4.1 Pharmacology

Sulfasalazine is one of the first antirheumatic drugs, and certainly the first specifically designed for the treatment of RA. In the late 1930's Professor Nana Svartz, rheumatologist at the Karolinska Institute of Stockholm, postulated that rheumatoid arthritis (RA) had a bacterial etiology and might benefit from the sulfa drugs then becoming available. She found that adding an antibiotic, sulfonamide, to the anti-inflammatory treatment with salicylates in RA, yielded little additional benefit and produced considerable gastrointestinal distress. Hoping that chemically combining the 2 drugs might at least attenuate gastrointestinal intolerance; she asked chemists from Pharmacia, a Swedish pharmaceutical company in Uppsala, to link sulfapyridine and 5-aminosalicylic acid in one compound, producing the drug now called sulfasalazine (SSZ) (73).

After ingestion of SSZ, the largest part (70-90%) of the molecules is split again by bacterial enzymes of the gut, into sulfapyridine (SP) and 5-aminosalicylic acid (5-ASA; mesalazine; mesalamine). The SP moiety is rapidly absorbed and metabolized by acetylation and glucuronidation by the liver after which it is excreted in the urine. The 5-ASA part is poorly absorbed and excreted in the faeces (74-76). Whether the parent drug SSZ and / or its metabolites SP and 5-ASA are responsible for its action remains unclear (76-79). The rate at which SP forms its main metabolite (N-acetyl-sulfapyridine) is dependent upon acetylator phenotype (74,80,81). In the Caucasian population there is an approximately equal distribution of fast and slow acetylators (74,76). The elimination half-life of SP is about 50-100% longer in slow acetylators, and slow acetylators have higher plasma concentrations of SP (74,82). There appears to be a relation between higher plasma SP concentrations and a higher prevalence of minor adverse effects observed in slow acetylators (74,82-85). A relationship between acetylator type and efficacy of SSZ treatment in RA has not been observed (80,81,84,85).

SSZ and its metabolite SP have antibacterial activities (77,78,86,87), but the lack of relation between changes in bacterial flora and clinical response (87), in addition with the absence of an antirheumatic effect of other sulfonamides (86), argue against relevance of these antimicrobial properties in antirheumatic treatment.

To date, the mode of action of SSZ is still under research and not fully understood. SSZ or its metabolites have multiple anti-inflammatory and immunomodulatory effects: influence

on cell adhesion molecules (88), on humoral (B-cells) (89-91), and on cellular (T-cells and cytokines of macrophage and T-cell origin) (89,92-94) immunity as reviewed by Smedegård and Björk (79). The effects of SSZ include inhibition of chemotaxis of inflammatory cells, inhibition of cytokine expression in mononuclear cells, inhibition of lymphocyte proliferation and activation (79), inhibition of osteoclast formation (95), inhibition of angiogenesis (94,96), and inhibition of folate-dependent enzymes (97,98). Clinical consequences of these immunomodulatory effects, showing as adverse events in some SSZ-treated RA and JIA patients, are described in **Chapter 3**.

Recent in vitro research demonstrated the anti-inflammatory effects of SSZ more specifically. Several mechanisms that result in a diminished production of proinflammatory cytokines such IL-1, IL6, and tumor necrosis factor α (TNF-α) have been observed (76,92-94). These mechanisms include inhibition of activation of nuclear factor kappa B (NFκB), thereby preventing the induction of transcription of NF-κB-responsive genes such as TNF-α (94,99,100), and induction of apoptosis in lymphocytes and macrophages (93). Clinically, SSZ unfolds its action 4 to12 weeks after the start of the therapy. In some patients, secondary SSZ resistance, i.e. loss of efficacy, develops after initial suppression of disease activity. This phenomenon appears, amongst others, to be related to genetic variation of individuals to generate T-cellular drug resistance by overexpression of specific drug efflux pumps (101). This mechanism is of importance since it might alter sensitivity of T-cells to other DMARDs (102,103).

4.2 Sulfasalazine in rheumatoid arthritis

The initial results of SSZ in treating RA were favorable as described by Svartz in 1948 (73). As a result of conclusions based on a badly designed study (104) and the spectacular results of the use of corticosteroids in RA treatment in the late 1940s (105), SSZ fell out of favor for the treatment of RA and for many years was used mainly in the treatment of inflammatory bowel diseases (106). In the late 1970s, when the long-term effects of steroid treatment became more apparent (107), Mc Conkey et al. in the UK revived interest in SSZ with encouraging reports that again showed the potential benefits of SSZ treatment in RA (108). Since then, several randomized controlled trials with SSZ in RA were performed which showed effectiveness of SSZ treatment as summarized by Weinblatt et al. (109). In addition to clinical improvement and adequate safety, retardation of radiographic progression was noted in SSZ treated RA patients (110,111). Currently, SSZ is a well-established DMARD used in the treatment of patients with RA either as monotherapy or in combination with other DMARDs, as was recently reviewed by Plosker and Croom (76).

4.3 Sulfasalazine in JIA

Reports of SSZ use in JIA first appeared in 1986 with the publication of an open study in 18 JIA patients by Özdogan (66) and have accumulated slowly since. In open studies and anecdotal reports concerning all types of JIA, a large variety of outcome definitions was used and the clinical efficacy varied accordingly. The treatment dose ranged between 30 - 80 mg/kg per day and was divided into two doses; in all cases the treatment dose was reached

in 3 to 6 weeks with gradual increments of the treatment dose over the weeks. In general, SSZ showed clinical benefit in a substantial number of JIA patients as is summarized in Table 2. (66-72,112-120). Most trials reported a reduction in the number of active joints and inflammatory parameters in the blood in a significant proportion of SSZ-treated patients. Some reports documented their own added definitions of 'improvement', 'partial' and 'complete remission' as outcome parameters (69-71,117-119). In most studies, a response to treatment was reported within 3 months. The length of the reported observations varied between 3 months and 5 years. Also patients with an initial good response to SSZ treatment, but with relapse of arthritis during the observation period, were occasionally reported (67,118). It was suggested that especially boys with late onset oligoarthritis showed a good clinical response (70,71,117); others however demonstrated that also young girls with oligoarticular onset ANA-positive JIA benefited from SSZ-treatment (118). Patients with systemic onset JIA experienced adverse events relatively often, and therefore the inclusion of these patients was stopped in 2 open studies (70,118).

To evaluate the efficacy and safety of SSZ treatment in oligoarticular and polyarticular subtypes of JIA, the Dutch Juvenile Chronic Arthritis Study Group initiated the first randomized placebo-controlled SSZ-trial in JIA patients, which is described in **Chapter 2**. So far, all of the aforementioned JIA studies reported on clinical efficacy of SSZ treatment and none of these studies included radiological outcome in its evaluation. To increase insight into the effects of SSZ-treatment, we included a radiological assessment in the placebo-controlled SSZ trial. Results of this radiological evaluation are presented in **Chapter 5 and 6**.

4.4 Tolerability of sulfasalazine

Approximately 20-30% of the patients with RA that were treated with SSZ experienced adverse events leading to discontinuation of therapy and almost all were reversible upon cessation of therapy (76,121-125). Most adverse evens occurred during the first few months after starting SSZ treatment and their occurrence decreased with continued use. The most commonly reported adverse evens included gastro-intestinal (GI) symptoms (nausea, vomiting, abdominal pain, dyspepsia, anorexia), central nervous system (CNS) symptoms (headache, dizziness), and mucocutaneous symptoms (rash, mouth ulcers). Other less frequently reported adverse events included hepatotoxicity (elevated liver enzymes, hepatic dysfunction), pulmonary symptoms (123,126), immune disorders (127,128), and lupus-like syndromes (129). Also hematological disorders, including leucopenia, thrombocytosis, macrocytosis, neutropenia, and anemia were described in 1-10% of the cases (76,121-124). Dose adjustment or cessation of therapy reversed the hematological disorders in most cases. GI and/or CNS phenomena comprised the majority of adverse events leading to termination of SSZ therapy (76,121,124).

The toxicity patterns observed in children and adolescents were similar to those observed in adults, as is summarized in Table 2. In children, intolerance involving the skin or GI tract (including liver enzyme abnormalities) occurred most frequently and were the main reasons for cessation of treatment. Observed leukopenia and neutropenia were reversible in all

cases, either by dose reduction (115,118) or cessation of treatment (66,70-72,118). In some studies, beside NSAIDs, other DMARDs were concomitantly used, including prednisone, hydroxychloroquine, auranofin, penicillamine, and methotrexate; this did not result in an increase of reported adverse events (66,68,118). Systemic onset patients most often showed symptoms of a toxic serum sickness-like reaction (fever, rash, abnormal liver enzymes, abdominal pain, lymphadenopathy, headache), however, these symptoms of hypersensitivity were also occasionally described in the first 3 weeks of SSZ treatment in patients with other JIA subtypes (70,72,118,130). In **Chapter 2,** we compare the adverse events observed in the placebo and SSZ treated patients during the SSZ-trial, and in **Chapter 3** we show the follow-up of patients who developed changes in serum immunoglobulin levels during SSZ treatment.

5. JIA therapy since the nineties

In the last 15 years, therapy for JIA has changed considerably. The multidisciplinary approach has remained with attention for physical, emotional and family support, but the treatment strategy has moved towards earlier institution of more potent DMARDs to suppress inflammation more aggressively, in line with treatment in adult RA (131,132). Four DMARDs have proven adequate efficacy and safety in randomized controlled trials: MTX, SSZ and etanercept against placebo and leflunomide equivalent to MTX (72,133-136). Efficacy of MTX was also tested in randomized trials in different subtypes of JIA and in different dosages ranging from 10-30 mg/m^2/week (134,137). Etanercept appeared a treatment option for patients with inadequate disease control with a weekly dose of at least 10 mg/m^2 MTX. Although other DMARDs and combinations of DMARDs are frequently used to treat JIA, the effectiveness of these treatments has not been evaluated in randomized controlled trials (131,132).

Intra-articular administration of corticosteroids has become a commonly used management technique to control disease locally, or as an adjunct to treatment in partially controlled disease (138,139). Evidence indicates that triamcinolone is more effective than other corticosteroids, and that the hexacetonide form has a more prolonged effect than the acetonide form (140).

Autologous stem cell transplantation (ASCT) was introduced as a treatment option for JIA patients who had failed all other treatment strategies or suffered from unacceptable side effects of such treatments. Although a number of patients has benefited from this procedure, ASCT carries a significant risk of transplant related morbidity and in some cases mortality (141).

In **Chapter 7** we describe the long-term outcome of patients who participated in the placebo-controlled SSZ trial. This cohort of patients is regarded as a representative group of patients who had a relative early opportunity of DMARD treatment in an active phase of their disease in the nineties and had access to the abovementioned therapeutic options. Specifically, we questioned whether the benefits of SSZ treatment during the trial were

sustained over time, in analogy to the results from the long-term follow-up study of the COBRA trial (Combinatietherapie Bij Reumatoide Artritis) in RA that showed a sustained difference in rate of radiological progression between the treatment groups (142,143).

6. Outcome Measures in Juvenile Idiopathic Arthritis

6.1. Assessment of disease activity and clinical response

Performing controlled trials in JIA has always been a difficult task for two main reasons: the relative rarity of the diseases, and the lack of reliable and internationally recognized outcome measures. To overcome these difficulties, an international network – the Pediatric Rheumatology International Trial Organization (PRINTO) – was founded in May 1996 in Pavia, Italy, with the goal of facilitating and coordinating international controlled clinical trials and outcome studies in children with rheumatic diseases.

In 1997, in collaboration with its North American Counterpart, the Pediatric Rheumatology Collaborative Study Group (PRCSG), PRINTO defined a core set of outcome measures and a preliminary definition of improvement in JIA for use in clinical trials (144). The approach used was similar to that developed by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) project that led to the WHO/ILAR core set and ACR definition of improvement for adult RA (145-147). The 6 variables that were chosen for the pediatric core set of outcome measures are shown in Table 3 and include: 1) physician global assessment of disease activity; 2) parent/patient assessment of overall well-being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) a laboratory marker of inflammation. After a validation study, this set of outcome measures and the preliminary definition of improvement were adopted by the ACR, and renamed the ACR Pediatric core set of disease activity measures and the ACR Pediatric 30 definition of improvement (ACR Pedi 30), respectively (148,149). According to the ACR Pedi 30, patients are considered as responders if they demonstrate at least 30% improvement relative to baseline in at least 3 of any 6 ACR Pediatric core set variables, with no more than 1 of the remaining variables worsening by more than 30%.

To describe functional outcome, the PRINTO/PRCSG researchers selected the Childhood Health Assessment Questionnaire (CHAQ)(150,151). The CHAQ has been shown to be a valid, reliable and sensitive tool for measuring functional status in children with arthritis, and yields a score of 0 (no disability) to 3 (very severe disability) (150). The CHAQ is an adaptation of the Stanford Health Assessment Questionnaire (HAQ) disability questionnaire designed to quantify disability in adults (152), and allows for age-appropriate activities ranging from childhood to adulthood (150). The data of the CHAQ and HAQ can be analyzed together (150,153). The CHAQ has been translated into many languages, and has been cross-culturally adapted and locally validated in several studies (151,154).

6.2 Radiological assessment in Juvenile Idiopathic Arthritis

JIA can lead to destructive lesions of joint cartilage and periarticular bone. A radiological assessment to evaluate damage to joints was not included in the evaluation of disease activity measures by PRINTO, because of the lack of availability of a standardized radiographic assessment score in JIA. As JIA therapy is moving towards early treatment with potentially toxic DMARDs, and more therapies are coming available, there is a growing need for a clear and reproducible radiological assessment standard both to select and to evaluate patients. Most published studies concerning radiographic joint damage in JIA are descriptions of the involved joints in different subtypes of JIA and elucidate the radiological signs of disease in the separate joints (155-157). Radiological changes most commonly considered as indicative of joint destruction in JIA include joint space narrowing, erosions, ankylosis and subluxation (156). In recent long-term outcome studies of patients with oligoarticular and polyarticular JIA joint damage was observed in up to 70% of the patients (158,159). The presence of radiographic damage appears to relate to disease duration and JIA subtype (6,156,159). In several studies, an association between presence of radiographic damage and functional disability, as observed in the CHAQ, was noted (9,159-161).

Pettersson and Rydholm made the first attempt to develop an objective radiological scoring system for joint abnormalities of the large joints in JIA (162,163). Their radiological classification contains scores for osteoporosis, growth disturbance, erosions, cyst formation and deformation of the joint surfaces of the large joints (shoulders, elbow, hips, knees and ankles). A score is given for the separate articulations within these joints. This scoring method leads towards a clear joint score, which might change over time, but is rather complicated to perform. Based on these studies, Dale described a pure morphological radiological staging system comparable with the Larsen score for the evaluation of the knee in JIA (164,165). Later, carpal length measured by plain film radiography (specifically the ratio of the carpal length to the length of the second metacarpal, often referred to as 'Poznanski score') (166) has been advocated for radiological assessment as a measure of cartilage integrity. Magni-Manzoni et al. used this method to evaluate polyarticular JIA patients with wrist involvement over time and showed that a reduced carpal length relatively early in the disease course related to long-term joint damage and functional disability (161). Evaluation of carpal length in JIA patients is not feasible in patients without wrist involvement, patients with advanced carpometacarpal erosions (which make it difficult to define bone ends), and patients with radiographic closure of the second metacarpal growth plate (around 14 years of age, and earlier in case of inflammation).

In order to develop a standardized assessment score for JIA to be applicable in trials, we studied the radiographs of the patients who participated in the SSZ-trial. For the development of this radiological outcome measure, we considered validity and applicability by the use of the 'OMERACT filter' (167). The OMERACT filter contains the following elements: *Truth*. Is the measure truthful, does it measure what is intended? The word contains issues of criterion (agreement with gold standard), and failing a criterion, face (the extend to which an instrument or criteria appear valid to those who are using it), content (comprehensiveness),

and construct validity (agreement between a theoretical concept and an instrument or procedure to measure it). *Discrimination.* Does the measure discriminate between situations of interest? The situation can be states at one time (for classification of prognosis) or states at different times (to measure change). The word captures issues of reliability and sensitivity to change. *Feasibility.* Can the measure be applied easily, given constraints of time, money and interpretability?

The development of a standardized method of assessment of radiographs (Dijkstra score) and radiographic change in JIA (Dijkstra composite score and progressor classification) are described in **Chapter 5 and 6.**

7. Disease course and outcome of JIA

The clinical disease course of JIA varies widely depending on the subtype of JIA, and is difficult to predict even within subtypes. Some patients develop remission before adult age, whereas others develop progressive joint destruction and serious functional disability (168-170). The reports on long-term follow-up of JIA show a significant range in terms of disease remission, functional ability and radiological damage because of differences in patient selection, methods for assessing outcome, criteria for remission and treatment, as was reviewed by Oen (11) and Adib et al. (171). In general, the occurrence of severe disability has declined over the years, but the proportion of patients who enter adulthood with active disease does not seem to be diminished (6,10). Most studies indicate that the majority of children with JIA have continuing or recurrent disease that extends into adulthood with persistent oligoarticular patients having the best perspectives (7,8,10,171,172).

Recent outcome reports of patients with JIA documented remission in 35-73% with oligoarthritis followed for 5-26 years, in 24-46% with polyarthritis followed for 7-26 years and in 33-76% with systemic arthritis followed for 26 years (7-9,158,168,172-174). Oen et al. documented that after a period of remission off medication the probability of disease relapse varied from 30-100% at 15 years (30% systemic JRA, 58% oligoarticular JRA, 62% polyarticular RF negative JRA, 100% polyarticular RF positive JRA) (7). Another expression of outcome of JIA is to assess patient disease course in terms of time spent in active disease and time spent in inactive disease. Patients can move back and forth between active and inactive disease during their disease course. In a follow-up study covering a time period of 4-22 years (median 6.5 years), Wallace et al. revealed that the majority of patients with extended oligoarthritis, polyarthritis and systemic disease spent nearly two thirds of their time with active disease. Overall, although 44% of patients achieved clinical remission off medication, this lasted less than 2 years in the majority of patients and 5 years in only 6% of patients (175).

Joint damage is another important outcome for children with JIA. There is a small number of reports addressing this issue, and these reveal joint space narrowing and erosions at anywhere from the first year of disease to later in 2-35% of patients with oligoarticular

disease, 13-77% of patients with polyarticular disease, and 19-75% of patients with systemic disease (9,158-160,172,176).

Persistent active arthritis is the main predictor of joint destruction (6,11,168,177). Several studies have tried to identify prognostic factors early in the disease course that relate to a persistent more destructive disease course. Complex interrelationships are found and predictive factors differ among onset subtypes (8,9,177-179). Late referrals, young age at onset, a greater severity or extension of arthritis at onset, symmetric joint disease, precocious wrist or hip involvement, presence of IgM-RF, a long duration of elevated erythrocyte sedimentation rate, and early radiographic changes have appeared to be associated with a more severe disease course in most subtypes (10,177-179).

In **Chapter 7** we describe the long-term outcome of the SSZ-trial participants. In this unique cohort of patients, we studied the long-term effects of a 6-month difference in initiation of DMARD treatment during an active phase of the disease. A follow-up study on the evaluation of radiographic damage is planned, but is beyond the scope of this thesis.

8. Contents of the thesis

In the early nineties, treatment of JIA was highly empirical and the outcome unsatisfactory. The aim of this thesis is to describe the efficacy and safety of SSZ treatment in children with JIA. We performed a multicenter, double-blind, randomized placebo-controlled trial in order to gain evidence for this treatment strategy in JIA. To evaluate effectiveness and safety, we used clinical and laboratory outcome parameters available at that time. To be able to evaluate efficacy of SSZ treatment including radiological outcome, we had to develop a radiological assessment score, since there were no validated scores available for use in JIA trials. In addition, we investigated whether the detection of autoantibodies, specifically anti-CCP, could be of help in the diagnosis of JIA, or in the identification of patients with a more destructive course of the disease. Finally, in a long-term outcome study, we analyzed whether the benefits of SSZ-treatment during the SSZ-trial were sustained over time.

In **Chapter 2,** we present the results of the first randomized, double-blind placebo-controlled SSZ study in patients with JIA.

In **Chapter 3,** we elaborate on aspects of dysimmunoglobulinemia, one of the adverse events observed during treatment with SSZ, in children with JIA.

In **Chapter 4,** we evaluate the presence of anti-CCP antibodies in children with different subtypes of JIA and relate these findings to the occurrence of radiographic damage in terms of joint space narrowing or erosions.

In **Chapter 5,** we introduce a standardized assessment method for radiographs of children with JIA. For the development of this method we used the baseline radiographs taken from the patients that participated in the placebo-controlled SSZ-trial. We describe the assessment of these radiographs for the presence of a comprehensive spectrum of JIA radiologic features, and we test this assessment method for its reliability, feasibility, and

correlation with clinical joint scores. All data of this chapter were collected together with Piet F. Dijkstra, who was a radiologist specialized in skeletal radiology and who died in June 2002. He spent most of his professional carrier in reading radiographs from patients with skeletal abnormalities and rheumatic diseases. In honour of him and of his huge knowledge of radiological manifestations of JIA, the standardized assessment was named after him: the 'Dijkstra score'.

In **Chapter 6,** we continue with the development of a standardized assessment method for radiographs in JIA, the 'Dijkstra score'. For this purpose, we used the study entry and 6 months' follow-up radiographs of the SSZ-trial participants. We evaluate the sensitivity to change of the Dijkstra score; we describe the development of a numeric composite score, the Dijkstra composite score, and a progressor classification scheme for use in JIA trials. The OMERACT filter of Truth, Discrimination and Feasibility is applied to the score.

In **Chapter 7**, we describe the long-term follow-up of the SSZ-trial participants. We contacted 99% of the former trial participants, collected their clinical and laboratory data, and reviewed 90% of them. We evaluated whether there is a difference in outcome between patients who were randomized to SSZ or placebo during the trial.

In **Chapter 8,** the results of the aforementioned studies are summarized, discussed and placed into the current perspective with increased treatment options since the introduction of anti-TNF medications. In addition, the relevance of inclusion of a radiological assessment into the outcome measures of JIA is outlined. Suggestions for future research are made.

Chapter 9 includes a summary and discussion in Dutch.

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Table 1. Classifications of childhood arthritis and clinical features*

JRA (ACR)	JCA (EULAR)	JIA (ILAR)
Onset age		
< 16 years	< 16 years	< 16 years
Minimum duration of disease for diagnosis		
6 weeks	3 months	6 weeks
Classification of subtype at disease duration		
6 months	3 months	6 months
Subtypes		
Systemic arthritis	Systemic arthritis	Systemic arthritis
Oligoarticular (Pauciarticular)	Oligoarticular (Pauciarticular)	Oligoarthritis
		- Persistent
		- Extended
Polyarticular JRA	Polyarticular JCA	Polyarthritis RF negative
(RF does not alter classification)	Juvenile rheumatoid arthritis	Polyarthritis RF positive
Excluded	Juvenile spondylarthropathies *(including juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter's syndrome and arthropathies of inflammatory bowel disease)*	Enthesitis related arthritis (ERA)
		Psoriatic arthritis
		Undifferentiated arthritis

*JRA: juvenile rheumatoid arthritis; ACR: American College of Rheumatology (12);
JCA: juvenile chronic arthritis; EULAR: European League Against Rheumatism (13);
JIA: juvenile idiopathic arthritis; ILAR: International League of Associations for Rheumatology (1);
RF: rheumatoid factor; Spondylarthropathy: inflammation of entheses and joints of the lumbosacral spine

Clinical features of JIA as defined by ILAR
Arthritis with / preceded by daily fever for at least 2 weeks' duration that is documented to be daily ('quotidian') for at least 3 days, and accompanied by one or more of the following: 1) evanescent (nonfixed) erythematous rash 2) generalized lymphe node enlargement 3) hepatomegaly and/or splenomegaly 4) serositis *Exclusions: a, b, c, d*
Arthritis affecting 1 – 4 joints during the first 6 months of disease. *Exclusions: a, b, c, d, e*
Affects no more than 4 joints throughout the disease course.
Affects more than 4 joints after first 6 months.
Affects 5 or more joints in first 6 months; test for RF is negative. *Exclusions: a, b, c, d, e*
Affects 5 or more joints in first 6 months; 2 or more tests for RF at least 3 months apart during first 6 months of disease are positive *Exclusions: a, b, c, e*
Arthritis and enthesitis or arthritis and enthesitis with at least 2 of the following: 1) presence of or a history of sacroiliac joint tenderness and/or inflammatory bowel disease 2) presence of HLA-B27 antigen 3) onset of arthritis in a male over 6 years of age 4) acute (symptomatic) anterior uveitis 5) history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative *Exclusions: a, d, e*
Arthritis and psoriasis, or arthritis and at least 2 of the following 1) dactylitis 2) nail pitting or onycholysis 3) psoriasis in a first degree-relative *Exclusions: b, c, d, e*
Arthritis that fulfills criteria in no category or in 2 or more of the above categories

Exclusions as defined in the ILAR classification (1):
The principle of this classification is that all categories of JIA are mutually exclusive. This principle is reflected in the list of possible exclusions for each category:

a. Psoriasis or a history of psoriasis in the patient or first-degree relative
b. Arthritis in an HLA-B27 positive male beginning after the 6th birthday
c. Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative
d. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.
e. The presence of systemic JIA in a patient.

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

Table 2. Studies on Sulfasalazine in the treatment of juvenile idiopathic arthritis*

Author	Year	Number of patients	Design study	Length study
Özdogan (66)	1986	18 all JRA subtypes (including 5 systemic)	Open label	4 - 14 months (mean 7.8)
Suschke (67)	1987	15 JCA (no systemic)	Open label	Not specified
Dulgeroglu (68)	1988	13 JRA (no systemic)	Open label	6 - 24 months (mean 11)
Grondin (69)	1988	12 JRA (including 1 systemic, 1 psoriatic arthritis)	Retrospective	0.5 - 18 months (mean 10)
Ansell (70)	1991	51 all JCA subtypes, (including 5 systemic)	Open label	12 months
Joos (71)	1991	41 all JCA subtypes (including 1 systemic)	Open label	3 - 36 months (median 12 months)
Settas (112)	1991	18 all JCA subtypes (including 3 systemic)	Open label	6 months
Suschke (113)	1992	11 all juvenile spondylarthropathy all HLA-B27+	Open label	12 months
Gedalia (114)	1993	10 oligoarticular onset JCA	Open label	4 - 24 months (mean 9 months)
Job-Deslandre (115)	1993	23 all juvenile spondylarthropathy	Open label	12 months
Romicka (116)	1994	28 all JCA subtypes	Open label	6 months
Frosch (117)	1995	48 all JCA oligo onset (40 late onset oligo)	Retrospective	Mean 64 weeks
Imundo (118)	1996	139 all JRA subtypes (including 5 systemic)	Open label	1 - 42 months (mean 13)
Huang (119)	1998	36 JCA (including 9 oligo-, 6 polyarticular onset and 21 spondylarthropathy)	Retrospective	1 month-8 years (mean 2.5 years)
Van Rossum (72)	1998	69 (35 SSZ and 34 PLAC) oligo- and polyarticular onset JCA	RPCT	24 weeks
Burgos-Vargas (120)	2002	33 (17 SSZ and 16 PLAC) all juvenile spondylarthropathy	RPCT	26 weeks

* PLAC: placebo; SSZ: sulfasalazine; oligo JCA: oligoarticular onset juvenile chronic arthritis (EULAR) (13); poly JCA: polyarticular onset juvenile chronic arthritis (EULAR); early onset: younger than 6 years of age; late onset: older than 8 years of age; spondylarthropathy: inflammation of enthesis and joints of the lumbosacral spine; ANA+ = anti nuclear antibody positive; HLA-B27+ = positive for HLA-B27 antigen; RPCT: randomized placebo-controlled trial;

† including active joints, painful joints, joints with limitation in motion

‡ the observed toxic adverse events included rash, fever and abnormal liver function (sometimes including lymphadenopathy) occurred within 20 days of SSZ treatment

	Response to SSZ	Stop Adverse events
	83% improved, joint counts† and ESR	1 patient leucopenia (in month 8)
	60% improved, active joints and ESR	1 patient rash, 1 patient anorexia
	85% improved at 6 months, active joints, ESR	None
	60% improved at 6 months, joint counts, ESR,	2 patients (not specified)
	40% improved joint counts and ESR; best in late oligoarticular onset HLA- B27+ patients	8 patients; including 2 systemics with rash, fever leucopenia, abnormal LF, headache‡; others with rash (2), leucopenia (1), diarrhea (2), migraine (1)
	80% improved joint counts, enthesiopathy, ESR; best in late oligo onset	4 patients: rash (1), leucopenia, (1), GI intolerance (1), agitation (1)
	61% improved, joint counts and ESR, best in oligoarticular onset	None
	72% improved, joint counts, entheseopathy, ESR	1 patient abdominal pain
	90% improved in all clinical joint scores, ESR	None
	78% 'very good'; 22% 'good', joint counts and ESR	None
	86% improved joint counts and ESR	5 patients (not specified)
	38% improved in early onset oligo; 78% improved in late onset oligo including HLA-B27+	3 patients (not specified)
	83% improved, joint counts and ESR; best in oligoarticular onset ANA+ girls and HLA-B27+	23 patients: rash (13), GI upset (4), leukopenia (2), headache (1). Rash, with fever and abnormal LF‡, in 2 systemic and 2 other patients
	60% of JCA and 68% of spondylarthropathy patients improved joint counts and ESR	1 patient diarrhea
	Active joints, overall severity joint scores, ESR, physicians' and patients' overall scores significantly better for SSZ patients	10 patients: anorexia (1), diarrhea (1), hematomas (1), abnormal LF (1 and 1 with ‡), leucopenia (2), hypoimmunoglobulinemia (3)
	Physicians' and patients' overall score significantly better in SSZ patients; no differences in joint scores	None

Table 3. Validated outcome measures for juvenile idiopathic arthritis, referred to as PRINTO score or ACR Pediatric 30 definition of improvement (ACR Pedi 30)*

1. Active joint count (joints with swelling or with limitation of motion and tenderness / pain on motion)
2. Joints with limited range of motion
3. Parent / patient global assessment (measured on a 0-10 visual analog scale)
4. Physician global assessment (measured on 0-10 visual analogue scale)
5. Laboratory measure of inflammation (erythrocyte sedimentation rate, C-reactive protein)
6. Functional assessment (CHAQ)

A patient is considered to have responded if there has been an improvement in at least 3 variables by at least 30% and worsening in not more than one variable by more than 30%.

*PRINTO: Pediatric Rheumatology International Trial Organization
ACR: American College of Rheumatology
ACR Pediatric 30 definition of improvement (144,148,149)
CHAQ = Childhood Health Assessment Questionnaire (150)

Chapter 2

Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study

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ABSTRACT

Objective. To assess the efficacy, tolerability and safety of sulfasalazine (SSZ) in the treatment of juvenile chronic arthritis (JCA).

Methods. We conducted a 24-week randomized, placebo-controlled, double-blind, multicenter study of patients with active JCA of both oligoarticular and polyarticular onset. Patients were treated with a dosage of 50 mg/kg/day of SSZ (maximum 2000 mg/day) or placebo. The efficacy variables were joint scores, physician's, parents' and patient's overall assessments, and laboratory parameters of inflammation.

Results. Of the 69 patients enrolled, 52 (75%) completed the trial. Six patients (18%) withdrew from the placebo group, and 11 (31%) withdrew from the SSZ group ($P = 0.18$). In the intention-to-treat analysis of end point efficacy, between-group differences were significant for the overall articular severity score ($P = 0.02$), all global assessments ($P = 0.01$) and the laboratory parameters ($P < 0.001$). Adverse events occurred more frequently in the SSZ group and were the main reason for withdrawal ($P < 0.001$), but were in all instances, these events were transient or reversible upon cessation of treatment.

Conclusion. The results of this first placebo-controlled study show that SSZ is effective and safe in the treatment of children with oligoarticular- and polyarticular-onset JCA, although it was not well tolerated in one-third of the patients.

INTRODUCTION

Second-line disease-modifying antirheumatic drugs (DMARDs) have been widely used in the treatment of juvenile chronic arthritis (JCA). The rationale for using these agents is based on their efficacy in the treatment of adult rheumatic diseases. Although open and retrospective studies have been conducted, only a few placebo-controlled studies of second-line antirheumatic drugs in JCA have been reported. These placebo-controlled studies have shown a disappointing efficacy of D-penicillamine, hydroxychloroquine (1), and oral gold (2), but have shown a positive effect of weekly administration of methotrexate (MTX) (3).

Sulfasalazine (SSZ) has been used extensively over the last 15 years in treating adults with rheumatoid arthritis (RA) (4,5). Several studies have shown a therapeutic advantage of SSZ over placebo in RA patients (6-10). In addition to improvement in clinical and laboratory indices of disease activity, the radiologic progression of erosions was also inhibited (9,11,12). The safety profile of SSZ has appeared to be acceptable (13-15). In children, SSZ is the most commonly used drug in the treatment of inflammatory bowel disease (16,17).

Anecdotal reports and open studies of SSZ treatment in children with JCA have shown encouraging results concerning the efficacy and safety of the drug (18-28). Serious side effects were noted in children with systemic-onset JCA (22,29). The lack of placebo-controlled studies with second-line agents in JCA and the efficacy of SSZ in RA prompted us to conduct a study designed to assess the efficacy, tolerability, and safety of SSZ in the treatment of children with oligoarticular- and polyarticular-onset JCA.

PATIENTS AND METHODS

Patients. The study was a cooperative effort by the Dutch Juvenile Chronic Arthritis Study Group, in which 7 pediatric rheumatology centers participated. The study was approved by the ethics committee in each participating center. The recruitment period was from August 1992 to December 1994.

To be eligible for enrollment, patients had to meet the European League Against Rheumatism (EULAR) criteria (30) for oligoarticular- or polyarticular-onset JCA. The age limits were 2-18 years, with onset of JCA before the age of 16. Further inclusion criteria were at least 1 joint with active arthritis (defined as the presence of swelling or limitation of motion [LOM], with either pain on movement or tenderness), and an insufficient response to nonsteroidal anti-inflammatory drug (NSAID) therapy at an optimal dosage for at least 3 months and, if applicable, to intraarticular corticosteroid injections. Patients who met the EULAR criteria for oligoarticular-onset JCA were included; due to the discrepancy between the American College of Rheumatology criteria for juvenile rheumatoid arthritis (31) and the EULAR criteria, spondylarthropathy patients were not excluded.

Exclusion criteria were previous treatment with SSZ, known hypersensitivity to sulfa preparations or salicylates; known glucose-6-phosphate dehydrogenase deficiency or porphyria, leucopenia <3.0 x 10^9/liter or granulopenia <1.0 x 10^9/liter or thrombocytopenia

<100 x 10^9/liter; liver transaminase levels more than twice the upper limit of normal, renal impairment defined as a creatinine clearance <90 ml/minute/1.73 m^2 (determined as an elevated serum creatinine level more than 2 SD above the mean value for age), or unwillingness or inability of parents or children to adhere to the protocol. Girls who might become pregnant (those who were postpubertal and, if sexually active, not practicing effective birth control) were also excluded.

Intraarticular corticosteroid injections were not permitted during the 8 weeks prior to the start of the study. Moreover, a 4-week washout period for all DMARDs was required.

Study design. The study was designed as a prospective, centrally randomized, double-blind, placebo-controlled, multicenter clinical trial of 24 weeks' duration. Informed consent was sought from the parents and patients according to the legal requirements. After consent was obtained, stratification was performed according to the JCA onset subtype (oligoarticular or polyarticular).

Method of randomization. After stratification for JCA onset type, a computer-generated randomization list was used to randomize patients to receive SSZ or placebo treatment. The randomization list was prepared by Pharmacia (Woerden, The Netherlands). Patients were assigned numbers according to the sequence in which they entered the study.

Monitoring of efficacy and safety. All patients were followed and monitored according to the same protocol. Each patient was scheduled to be examined or to receive laboratory tests during a total of 9 visits over a 24-week period. Six visits to the physician were scheduled: 1 at the start of the study, followed by 1 every 4 weeks during the first 12 weeks and 2 every 6 weeks during the subsequent 12 weeks. Physical and laboratory assessments of rheumatic disease activity and drug safety were completed at each clinic visit. Three separate laboratory checks for safety were scheduled between visits to the physician in the first 12 weeks. For a given patient, all rheumatologic examinations and assessments of laboratory results were performed in the individual's center.

Three clinical indices of articular inflammation were used: joint swelling (graded as 0 = none; 1+ = mild, but obvious, synovial swelling or effusion and bony landmarks visible; 2+ = moderate swelling and definite obscuring of bony landmarks; 3+ = severe swelling and no discernible bony landmarks); pain on motion and/or joint tenderness (graded as 0 = none; 1+ = mild pain with no subjective reaction [reported by the patient only after being asked]; 2+ = moderate pain [patient winces or withdraws or reports pain without being asked]; 3+ = marked pain [notable withdrawal of the joint when palpated or moved]); and LOM (graded as 0 = full range of motion; 1+ = 25% limitation; 2+ = 50% limitation; 3+ = 75% limitation; 4+ = no motion possible).

In addition to these indices, the total number of joints with active arthritis and the sum of all the severity ratings of the 3 clinical indices of articular inflammation for each joint (referred to as the overall articular severity score) (3) were recorded. At each follow-up visit,

the examining physician documented his or her general impression of disease activity (0+ = none; 1+ = very low; 2+ = low; 3+ = moderate; 4+ = active; 5+ = very active). In addition, the parent, and if applicable the patient, recorded a categorical global rating of the child's disease activity (1+ = very low; 2+ = low; 3+ = moderate; 4+ = active; 5+ = very active).

At each visit to the physician, adverse events (defined as any untoward medical occurrence during treatment) were monitored by asking parents and patients open-ended questions to identify any problem that had occurred since the previous visit. Specific inquiries were made about the occurrence of skin rash, pruritus, anorexia, nausea, vomiting, gastrointestinal discomfort, diarrhea, general feeling of unwellness, change in behavior, headache, and fever.

At study entry, HLA-B27, antinuclear antibody, and rheumatoid factor were measured. Patients were monitored by several laboratory tests as follows: measurement of hemoglobin, mean red blood cell volume, number of reticulocytes, white blood cell count and differential cell count, number of platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase, serum creatinine, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, gamma glutamyl transpeptidase, alkaline phosphatase, folic acid and urinalysis. Serum immunoglobulins were measured at study entry and after 12 and 24 weeks of treatment.

Because of the possibility of adverse events during the trial, one of us (BACD) acted as safety monitor with the independent support of one of the members of the official Dutch Office of Side Effects.

Radiologic assessment. At study entry and after 24 weeks of treatment, radiographs of all the affected joints (either tender, painful, swollen or limited in motion) were obtained. After completion of the trial, the radiographs were all read by one radiologist (PFD) who was not made aware of the treatment given to the patients. All radiographs were viewed under identical conditions and in chronologic order for each patient. The following joints were evaluated separately at the 2 time points: the cervical spine, mandibles, shoulders, elbows, hands/wrists, sacroiliac joints, hips, knees, ankles, and feet.

Since there is no validated roentgenologic scoring system available for JCA, we developed a standardized scoring list for this trial that was applicable to all of the joints considered. Scores were assigned for soft tissue swelling, osteoporosis, joint space narrowing, enlargement or other growth disturbances, bone cysts, erosions and joint alignment. A combination of RA radiologic joint scores were used as guidelines. The method of Rau and Herborn (32) was used for scoring soft tissue swelling, joint space narrowing, osteoporosis and erosions, and that of Fuchs et al (33) for scoring joint malalignment. Two radiographs of the same joint were compared, and the radiologist assigned scores to reflect the evolution of the change in the joints: score 00 = unaffected, or normal on both occasions; score 0 = affected, but unchanged; score 1+ = improvement; and score 1- = deterioration. All joints radiographed at the beginning and at the end of the trial were evaluated in this manner; when films were missing or had technical shortcomings, the films were scored as "not evaluable".

Study drugs and dosages. SSZ was provided in the form of capsules in doses of 125 mg and 250 mg, and plain tablets of 500 mg each, with corresponding placebo capsules and tablets. The production of the study medications, packaging, labeling, and distribution to the cooperating centers were done by Pharmacia. After enrollment of the patient in the study, the medication was sent to the hospital pharmacy and dispensed by the hospital pharmacist to the patient as requested by the investigator. The dosage of SSZ for this study was 50 mg/kg/day administered in 2 doses, with a maximum of 2000 mg/day. The treatment was started with one-fourth of the total dose, and increased weekly by increments of one-fourth the calculated dose. Compliance was verified by tablet counts. In the case of intolerance to the daily dose, the dose frequency could be changed or a dose adaptation could be made to the highest dose tolerated, but no be lower than 50% of the initial total prescribed dose. Investigators were instructed not to break the code until completion of the study, except in cases of medical emergency.

Concurrent medications and therapy. NSAIDs had to be continued in type and dose during the study period. Corticosteroids (oral or intra-articular injections) or other DMARDs were not permitted during the study period. Other therapy considered necessary for the patient's welfare was allowed to be given at the discretion of the investigator. All such therapy had to be recorded in the case record form. The patients were instructed to continue their programs of physical and occupational therapy during the study.

Response variables. The primary clinical efficacy variable was response as defined by improvement by 2 grades in the severity score for joint swelling or a score of 0 in 50% or more of the joints that were involved at baseline, and, if applicable, development of disease activity in ≤10% of the other joints, with the restriction that the number of deteriorated joints had to be ≤50% of the number of improved joints. The secondary clinical efficacy variables included the overall articular severity score (sum of all scores for swelling, tenderness/pain and LOM), the patient's general impression of disease activity (score 1-5), the parents' general impression of disease activity (score 1-5), and the physician's general impression of disease activity (score 0-5). Other outcome measures were the laboratory parameters (ESR, CRP) and the radiological evaluation.

The core set of Pavia criteria (preliminary definition of improvement in juvenile arthritis) (34) was also applied to our data. To be classified as improved in this Pavia core set, patients must have at least 30% improvement from baseline in 3 of 6 variables, with no more than 1 of the remaining variables worsening by more than 30%. Variables included in the core set are: 1) physician's global assessment, 2) parents' global assessment, 3) the number of joints with active arthritis, 4) the number of joints with LOM, 5) the ESR, and 6) functional ability (34). Since we did not collect data on functional ability, we classified our patients as improved according to the Pavia core set when patients showed at least 30% improvement from baseline in 3 of 5 variables of the core set, and not more than 1 of the core set parameters could be worsened by more than 30%.

Statistical analysis. Quantitative variables were expressed as the mean and standard deviation (SD), and qualitative variables with numbers and percentages. When necessary, quantitative variables were logarithmically transformed. The treatment groups were compared with respect to baseline demographic, clinical, and disease characteristics using Student's *t*-test, chi-square test, and Mann-Whitney test. Adjustment for disease onset was performed with two-way analysis of variance (ANOVA) and logistic regression analysis. The measurements of disease activity and laboratory variables were analyzed on an intention-to-treat basis using mixed-model ANOVA on the change values with the baseline measurements as covariate, with adjustment for onset type. When appropriate, the interaction between posttreatment and baseline values was assessed. The treatment response course during the trial was analyzed with a logistic regression model with random patient effects. A *P* value of 0.05 or less was considered significant.

The main analysis was an intention-to-treat analysis. All patients were assessed at each of the 6 time points whether or not they were still receiving treatment. It was expected that 25% of the patients in the placebo group and 60% in the SSZ group would respond. With a power of 80% and a significance level of 0.05, it was calculated that at least 32 patients had to be randomized to each treatment group. We expected a 10% dropout rate, and therefore aimed for a total of 70 patients. The treatment protocol was varied only after all analysis had been performed.

RESULTS

Patient characteristics and compliance. A total of 69 patients (46 girls, 23 boys) were enrolled in the trial. The JCA onset type was oligoarticular in 37 patients and polyarticular in 32 patients. The SSZ and placebo treatment groups were balanced in terms of their demographic, clinical, and disease activity characteristics, with the exception of the significantly lower levels of IgM rheumatoid factor in the SSZ group (Tables 1 and 2). No significant differences were observed in family history or in concomitant diseases between the 2 treatment groups (data not shown). Two patients had taken systemic corticosteroids and had stopped this treatment 4 and 8 months, respectively, before study entry. Four patients had taken hydroxychloroquine and one patient had taken intramuscular gold before start of the study. These DMARDs were stopped due to inefficacy at least 4 weeks before study entry. All patients had taken NSAIDs. Estimates of patient compliance were made based on pill counts; 83% of patients (57 of 69) had a compliance rate of >80%; 6% (4 of 69) had a compliance rate <80%, and in 11% of patients (8 of 69), drug accountability was not deducible. No code was broken before all analyses had been performed.

Study withdrawals. Of the 69 enrolled patients, 68 qualified for the intention-to-treat analysis of efficacy; 1 patient was excluded from the efficacy analysis because of ineligibility. Among the 69 randomized patients, 52 (75%) completed the 24-week trial, including 32

Table 1. Demographic and clinical characteristics at study entry according to treatment group*

	Treatment group	
Characteristic	Placebo (n = 34)	SSZ (n = 35)
Mean ± SD age (range), years	9.7 ± 3.6 (2.5-15.1)	8.4 ± 4.4 (2.5-17.6)
Females, no. (%)	23 (68)	23 (66)
Median disease duration (IQR; range), months	16.7 (7-37; 5.5-142.1)	26.8 (14-56; 4.7-176.1)
Polyarticular onset, no. (%)	16 (47)	16 (46)
Oligoarticular onset, no. (%)	18 (53)	19 (54)
>4 active joints at study entry, no. (%)	22 (65)	21 (60)
Antinuclear antibodies present, no. (%)	15 (50)	18 (53)
IgM rheumatoid factor present, no. (%)	7 (23)	2 (6)
Local corticosteroid use ever, no. (%)	14 (41)	16 (46)
DMARD use ever, no. (%)	1 (3)	4 (11)
Systemic corticosteroid use ever, no. (%)	2 (6)	0 (0)
HLA-B27 positive, no. (%)	4 (12)	7 (20)

* SSZ = sulfasalazine; IQR = interquartile range; DMARD = disease-modifying antirheumatic drug (second-line antirheumatic drug).

Table 2. Disease activity characteristics at study entry, according to treatment group*

	Treatment group	
Variable	Placebo (n = 34)	SSZ (n = 35)
Number of swollen joints	6 (2-10)	5 (2-11)
Swollen joints severity score	9 (3-12)	7 (3-16)
Number of tender/painful joints	5 (0-10)	2 (0-5)
Number of joints with LOM	4 (1-8)	4 (1-6)
Overall articular severity score	20 (7-33)	19 (6-30)
Number of active joints	7 (3-12)	5 (2-11)
Patients' score of disease activity	3.2 ± 0.9	2.8 ± 0.8
Parents' score of disease activity	3.3 ± 0.9	3.1 ± 0.7
Physicians' score of disease activity	3.6 ± 0.8	3.2 ± 0.9
ESR, mm/hour	28 (11-53)	25 (11-38)
C-reactive protein, mg/liter	10 (1-37)	5 (1-19)

* Values involving the joints and laboratory values are the median (interquartile range). The remaining values are the mean ± SD. SSZ = sulfasalazine; LOM = limitation of motion; ESR = erythrocyte sedimentation rate.

(86%) with oligoarticular-onset JCA and 20 (63%) with polyarticular-onset JCA. The reasons for premature discontinuation of the study drug were adverse events (10 patients, all receiving SSZ), insufficient efficacy (3 patients, all receiving placebo), consent withdrawn (2 patients, both receiving placebo), ineligibility (1 patient in the placebo group), and lost study interest (1 patient in the SSZ group).

Efficacy. *Change of the disease activity characteristics and global assessments.* The results of the intention-to-treat analysis of the 2 groups are given in Table 3. Statistically significant

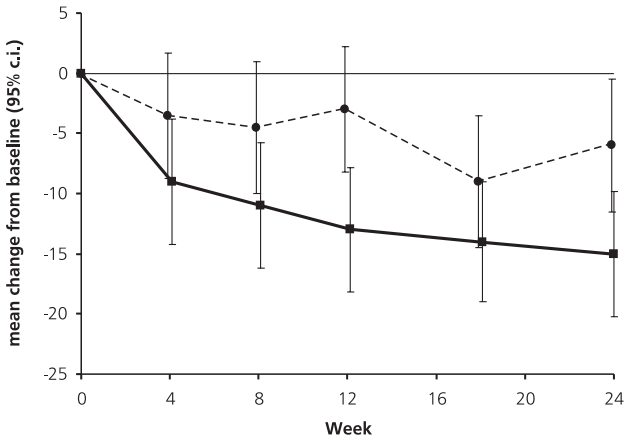

Figure 1. Changes in the overall articular severity score following treatment with sulfasalazine (■) compared with placebo (●). Bars show the mean and SD. 95% c.i. = 95% confidence interval.

reductions were seen in the SSZ treatment group compared with the placebo group in the number and severity score of swollen joints, overall articular severity score, number of active joints, scores of disease activity (patient, parents and physician), ESR, and CRP level. The other parameters of disease activity (number and severity score of tender/painful joints, and number and severity score of joints with LOM) were reduced in the SSZ group compared with the placebo group, but the between-group differences in these parameters did not reach statistical significance (Table 3).

Examples of the time course of effect of SSZ treatment are shown in Figures 1 (overall articular severity score) and 2 (physicians' score of disease activity). Other disease activity characteristics showed a similar pattern. Within a month after starting SSZ treatment, disease activity characteristics had decreased and the global assessments started to improve. This improvement was continued up to 3 months after starting SSZ treatment, and a lower

Table 3. Changes in the indices of articular disease from baseline to final visit in the intention-to-treat analysis*

	Treatment group		
Variable	Placebo (n = 34)	SSZ (n = 35)	*P*†
Number of swollen joints	-1.43 (1.18)	-5.10 (1.13)	0.025
Swollen joints severity score	-2.39 (1.27)	-7.04 (1.21)	0.008
Number of tender/painful joints	-1.81 (1.06)	-4.11 (1.02)	0.12
Number of joints with LOM	-1.97 (0.80)	-2.49 (1.12)	0.64
Overall articular severity score	-6.17 (2.87)	-15.14 (2.76)	0.020
Number of active joints	-0.78 (1.22)	-5.54 (1.16)	0.005
Patients' score of disease activity	-0.24 (0.18)	-0.92 (0.18)	0.008
Parents' score of disease activity	-0.44 (0.16)	-0.98 (0.14)	0.010
Physicians' score of disease activity	-0.99 (0.19)	-1.95 (0.18)	0.0002
ESR, mm/hour	-0.04 (0.08)	-0.74 (0.07)	<0.0001
C-reactive protein, mg/liter	-0.01 (0.14)	-0.45 (0.14)	0.030

* Values are the mean (SEM) change from baseline. See Table 2 for definitions.
† Student's t-test.

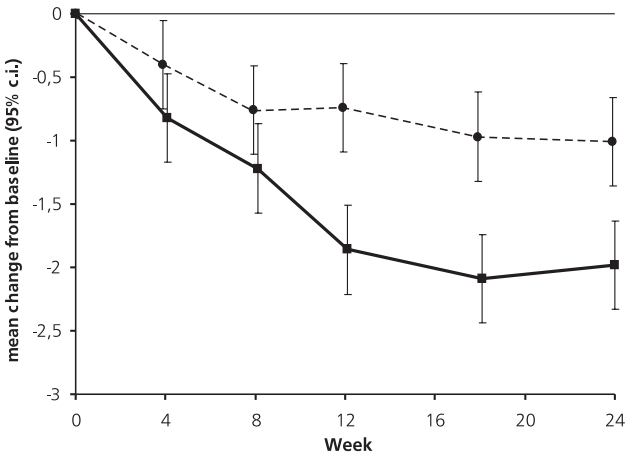

Figure 2. Changes in the physicians' score of disease activity following treatment with sulfasalazine (■) compared with placebo (●). Bars show the mean and SD. 95% c.i. = 95% confidence interval.

level of disease activity was maintained thereafter. In the placebo group, the disease activity parameters also declined during our study, but less consistently when compared with the SSZ treatment group. The SSZ treatment effect was not significantly different between patients with oligoarticular- and polyarticular-onset disease (data not shown).

Response in individual patients. The proportion of patients responding to treatment was consistently higher in the SSZ-treatment group than in the placebo group ($P < 0.01$). At the final visit (week 24), 69% (9% SEM) of the SSZ-treated patients had responded to treatment (according to our definition of response), whereas a response was seen in 45% (9% SEM) of the placebo-treated patients ($P = 0.06$) (Figure 3). There was no significant difference between oligoarticular- and polyarticular-onset patients with regard to the percentage of responding patients according to our definition of response to treatment ($P = 0.34$).

When the core set of Pavia criteria (preliminary definition of improvement in juvenile arthritis) (34) was used to define improvement and this core set was applied to our variables, patients receiving SSZ improved significantly more ($P < 0.001$) than patients receiving placebo over the entire study period (Figure 4). At the final visit (week 24), 44% (9% SEM) of the

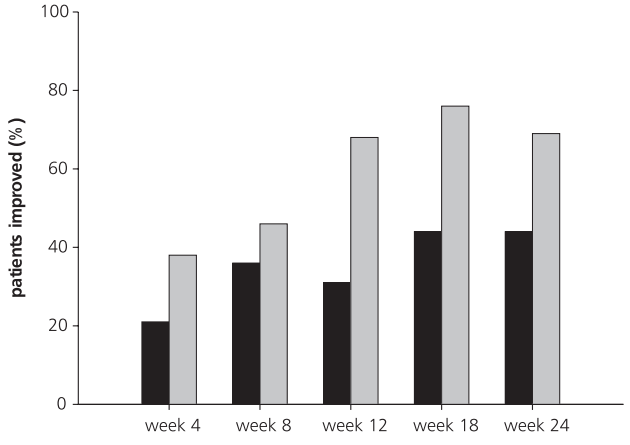

Figure 3. Patients' response to sulfasalazine therapy (■) as compared with placebo (■). Response was defined as improvement in the severity score of joint swelling by 2 grades or a score of 0 in 50% or more of the joints involved at baseline, and, if applicable, development of disease activity in ≤10% of the other joints, with the restriction that the number of deteriorated joints had to be ≤50% of the number of improved joints.

SSZ-treated patients and 21% (8% SEM) of the placebo-treated patients (P = 0.049) were classified as improved according to the core set of Pavia criteria. There was no significant difference (P = 0.67) between oligoarticular- and polyarticular-onset patients with respect to the percentage of patients responding to SSZ-treatment when applying the core set of Pavia criteria to our variables.

Radiologic evaluation. We obtained radiographs from the 68 evaluable patients. Three patients had incomplete sets. The total number of comparable joint groups (maximum of 19) varied in our patient population from 2 to 15. The mean number of joints that were scored as improved by the radiologist in the placebo treatment group was 0.53 (range 0-3), versus 0.71 (range 0-3) in the SSZ treatment group. The mean number of joints that were scored as not changed was 4.3 (range 0-12) in the placebo group versus 5.1 (range 1-10) in the SSZ treatment group. The mean number of joints that were scored as deteriorated was 1.23 (range 1-10) versus 0.71 (range 0-4) in the SSZ treatment group. None of the results were significantly different.

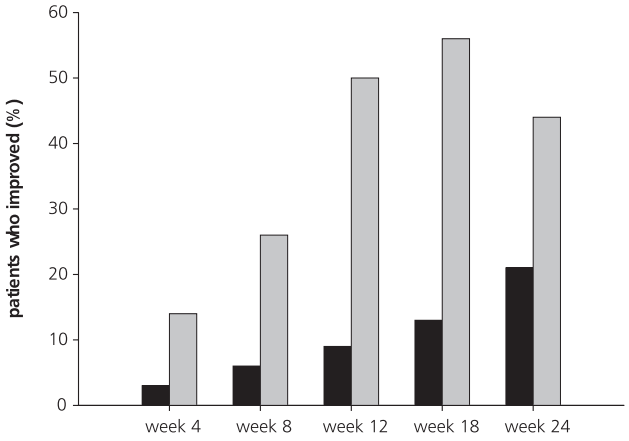

Figure 4. Patients' response to sulfasalazine therapy (▒) as compared with placebo (■). Response was defined according to the preliminary definition of improvement in juvenile arthritis (known as the Pavia criteria) (34).

Tolerability and safety. The type and frequency of adverse events are shown in Table 4. Several adverse events occurred during the trial; 30 patients (86%) in the SSZ-treatment group reported at least 1 adverse event versus 29 (85%) in the placebo group (P = 0.96). These adverse events resulted in withdrawal of 10 patients, all of whom were from the SSZ treatment group (P < 0.001). In 1 patient in the SSZ treatment group, the adverse events were graded as serious (toxic reaction with anorexia, nausea, abdominal complaints, general feeling of unwellness, headache, fever, rash, cervical lymphadenopathy, increased liver transaminase levels). All adverse events were reversible after discontinuation of treatment. Gastrointestinal complaints occurred in 42 (61%) of the 69 patients, of whom 24 were in the SSZ treatment group and 18 in the placebo group (P = 0.18). Anorexia and abdominal discomfort were the most frequent gastrointestinal disorders observed, with a somewhat higher frequency in the SSZ treatment group compared with the placebo group (P = 0.014 and P = 0.17, respectively). Skin rashes occurred more often in the SSZ treatment group than

Table 4. Type and frequency of the main reported adverse effects in the 69 patients, by treatment group*

	Treatment group	
Side effect	Placebo (n = 34)	SSZ (n = 35)
Gastrointestinal		
Anorexia	7	17 (1)
Nausea	4	10
Abdominal discomfort	11	17
Diarrhea	5	5 (1)
Skin disorders		
Rash	3	9
Hematomas	0	2 (1)
CNS disorders		
Headache	5	9
Dizziness	1	0
Laboratory disorder		
Liver transaminases elevated	0	2 (2)
Leukopenia	0	2 (2)
Hypo-immmunoglobulinemia	0	4 (3)

* Values are the number of patients with the adverse event (number of patients with premature discontinuation of study drug because of the adverse event). SSZ = sulfasalazine. CNS = central nervous system.

in the placebo group (P = 0.07), but were not specific. Five of the 10 children who finally had to stop SSZ medication had developed skin rashes, but none of these was severe nor the main reason for withdrawal. Three of the 10 patients who had to discontinue the study drug did so because of the occurrence of adverse events, while the other 7 children had to stop because of a combination of clinical symptoms and abnormal laboratory findings.

Laboratory evaluation of safety. Patients who received SSZ treatment experienced significant changes during the trial in several laboratory measurements: increases in the mean red blood cell volume and number of reticulocytes, a decrease in the number of leukocytes, a decrease in the serum level of folic acid, elevated levels of serum alkaline phosphatase and glutamic pyruvic transaminase, and a decrease in the serum levels of immunoglobulins A, M, and G (Table 5). In 7 patients from the SSZ-treatment group laboratory abnormalities were the main reason for withdrawal. These findings were leukopenia in 2 patients, liver transaminases elevated more than 3 times over the baseline value in 2 patients, and very low immunoglobulin (Ig) A levels in 3 patients. In the other patients, the laboratory changes were judged to be clinically unimportant. Two patients developed clinical symptoms of easily bruising. In 1 patient, the symptoms were so annoying (normal platelet counts and normal coagulation study findings, but a bleeding time over 8 minutes) that it necessitated study withdrawal. After discontinuing the SSZ and NSAID (Naproxen) treatment, the symptoms disappeared.

Table 5. Changes in the immunoglobulin levels from baseline to final visit*

	Baseline		Change		
Variable	Placebo (n = 34)	SSZ (n = 35)	Placebo (n = 34)	SSZ (n = 35)	*P*†
IgA, g/liter	2.04 (0.94)	1.62 (0.79)	0.16 (0.11)	-0.70 (0.10)	<0.001
IgG, g/liter	16.05 (4.30)	13.42 (3.79)	-0.10 (0.48)	-2.85 (0.44)	<0.001
IgM, g/liter	1.55 (0.60)	1.57 (0.69)	0.09 (0.07)	-0.50 (0.07)	<0.001

* Values are the mean (SEM). SSZ = sulfasalazine. Ig = immunoglobin.
† By mixed-model analysis of variance, adjusted for baseline values.

Most of the adverse events in this study were reported within the first month of the study. However, in the SSZ treatment group, only 2 patients withdrew from the study because of adverse events within the first month (both patients had a toxic reaction with malaise, skin rash, and increased liver enzyme levels), while 2 other patients withdrew during the second month (1 with anorexia and malaise, and 1 with leukopenia), 2 in the third month (1 with easily bruising, and 1 with leukopenia) and 4 even later in the study (1 with ongoing malaise and diarrhea, and 3 others with very low IgA levels).

DISCUSSION

The main conclusion from this first placebo-controlled, double-blind study of SSZ is that SSZ is an effective second-line antirheumatic drug in the treatment of both oligoarticular- and polyarticular-onset JCA. The efficacy of SSZ over placebo was assessed according to the conventional parameters of disease activity, radiologic changes, and the recently developed response criteria (34). A significant reduction in both the severity and number of swollen joints, the number of active joints, and the overall articular severity score was seen in patients who received SSZ treatment. A progressive and significant decrease was shown in the acute-phase reactants in the SSZ-treated patients. The good clinical response to SSZ treatment was also reflected in the global assessments by the patients, parents and physicians. The clinical response in all variables studied was observed within 3 months of treatment and was maintained during the study period. To date, our results are consistent with those of previous studies, all of which were open studies (18-28,35). The efficacy of SSZ treatment in both oligoarticular- and polyarticular-onset JCA as demonstrated in the present study is a finding that is in contrast with the results of open studies by Joos et al (23), Ansell et al (22), and Frosch et al (27). Those investigators all reported greater effectiveness of SSZ treatment in oligoarticular-onset patients, particularly in boys who were HLA-B27 positive. These differences might, in part, be explained by the differences in the demographic and disease characteristics of the study patients. We excluded patients who were receiving oral prednisone. We cannot rule out the possibility that, with the use of this exclusion criterion, the more severe forms of the disease might have been underrepresented.

Studies in adults with RA have shown an inhibition of radiologic progression of the disease in SSZ-treated patients (9,11,12). The effect could be demonstrated within 24 weeks

of treatment (9,12). We could not confirm this observation in our JCA study, in which only a tendency toward more deterioration was noted in the placebo treatment group. An explanation might be that our scoring method (improved, unchanged, deteriorated) was not sensitive enough to detect specific changes. Description of radiologic changes in JCA is difficult, since there is still no validated radiologic scoring system for JCA.

This study reports the effectiveness of SSZ treatment on clinical and laboratory parameters, not on functional status. At the time this study was undertaken, there were no validated functional outcome measures available (36). In spite of the lack of functional outcome measures, we applied the latest definition of improvement in JCA to our data (34); these criteria confirmed the efficacy of SSZ treatment. It is unlikely that the addition of functional status would have changed the overall results of the study.

Although SSZ proved to be a beneficial drug, its administration was accompanied by many adverse events. Ten (29%) of the 35 SSZ-treated patients developed adverse events that led to premature discontinuation of the study drug. Our withdrawal rate of 29% for toxicity is higher than that reported in open studies of SSZ treatment in JCA, in which withdrawal rates of 10-20% have been observed (23,35). In our study, we used the relatively high SSZ dosage of 50 mg/kg/day, whereas others have used 30-50 mg/kg/day. Moreover, all patients kept their dosage of NSAIDs unchanged during the study period. This could all have contributed to the higher side effect profile in our study compared with that in other SSZ studies performed in JCA patients. The type and frequency of reported side effects in our patients are comparable with those reported in studies of adults with RA treated with SSZ. In those studies, a withdrawal rate of 20-30% has also been noted (15,36,38). Our study confirms that adverse reactions resolve rapidly on withdrawal of the drug (15,35). In 1 of our patients, the adverse reaction was graded as serious and resembled an idiosyncratic reaction (39). This type of serious reaction can be expected to occur within the first 3 weeks of therapy. Therefore, it is necessary to monitor patients closely after initiation of SSZ therapy. However, we found that some of the adverse reactions that necessitated drug withdrawal (such as leukopenia or hypo-immunoglobulinemia) occurred several months into the regimen, indicating that laboratory values should be checked regularly during administration of SSZ treatment.

The efficacy-toxicity balance of SSZ in JCA has to be weighed against that of other second-line antirheumatic drugs. Efficacy in JCA has been proven for MTX (3) while other drugs (D-penicillamine, hydroxychloroquine, oral gold) failed to demonstrate convincing efficacy (1,2). When comparing our study with the placebo-controlled, low-dose MTX study by Giannini et al (3), we note several differences and several similarities. The demographics of the 2 study populations differ; our study included children with a shorter disease duration, fewer joints with active arthritis, lower overall articular severity score, use of corticosteroids was not allowed in our patients, and our study did not include children with systemic-onset JCA. At the end of both studies, significant improvement was shown in the global assessments and in the overall articular severity score. The individual responses in both studies were significantly higher in the treatment groups compared with the placebo groups. Both studies demonstrated highly comparable effectiveness in terms of their respective treatments. The

time course of effect was shorter in the SSZ-treated patients. The number of adverse events was lower in the MTX-treated patients. Thus, a direct, comparative study of the efficacy of low dose MTX and SSZ is warranted.

Over the last few years, there has been a move toward earlier treatment of RA with second-line antirheumatic drugs in an attempt to control synovitis before joint damage occurs (40,41). This change toward earlier aggressive treatment has also permeated the approach to treatment of JCA (42). Since SSZ has an acceptable risk-benefit ratio and the patient's condition improves rather early after starting treatment, one could argue for using this drug early in the course of oligoarticular- as well as polyarticular-onset JCA. All side effects are reversible, and when laboratory screening is done regularly, no serious toxicity is to be expected.

Future studies on SSZ treatment should determine whether SSZ can induce remission, and whether it can prevent growth disturbances or development of erosions and subsequent destruction of the joints. Its place in developing the optimal combination therapy for JCA has yet to be determined.

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Chapter 3

Effects of sulfasalazine treatment on serum immunoglobulin levels in children with juvenile chronic arthritis

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ABSTRACT

This article describes the effects of sulfasalazine (SSZ) treatment on serum immunoglobulin (Ig) levels in 6 children with oligoarticular- or polyarticular onset juvenile chronic arthritis (JCA). None of the children who developed dysimmunoglobulinemia during treatment showed clinical symptoms of this adverse event, in particular none developed severe infections. All patients regained normal immunoglobulin levels after discontinuing SSZ treatment. One patient with a partial IgA deficiency at the start of SSZ treatment showed a slow increase in the IgA level during treatment. During follow-up (4-6 years), one patient spontaneously developed a dysimmunoglobulinemia and one patient developed diabetes mellitus. Based on these case reports and review of the literature we advocate monitoring of serum immunoglobulin levels while on SSZ treatment.

INTRODUCTION

After sulfasalazine (SSZ) had become an established drug in the treatment of rheumatoid arthritis (1-4), it has also occasionally been included in the treatment of oligoarticular- and polyarticular-onset juvenile chronic arthritis (JCA) (5-12). Its benefits in the treatment of JCA were recently established in a placebo-controlled double-blind study (13). Sulfasalazine is a conjugate of 5-aminosalicylic acid, a salicylate analogue, and sulfapyridine, a sulfonamide linked by an azo bond. After ingestion hardly any of the intact drug is absorbed. It is split in the colon by bacterial azoreductases into sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is well absorbed and metabolized by acetylation and glucuronidation in the liver. The absorption of 5-aminosalicylic acid is poor (14). The mode of action by which SSZ reduces disease activity is unclear. SSZ or its metabolites appear to have multiple anti-inflammatory and immunomodulatory effects, including influence on prostaglandin and leukotriene metabolism, on cell adhesion molecules, on humoral (B-cells) and on cellular (T-cells and cytokines of macrophage- and T-cell origin) immunity (15,16). In several studies it has been reported that rheumatoid arthritis (RA) and JCA patients treated with SSZ show a gradual decline in serum immunoglobulines (3,9,13,17-19). Development of low levels of individual immunoglobulins or hypogammaglobulinemia has occasionally been described in RA and JCA patients treated with SSZ (13,17,18,20,21). However, measurement of immunoglobulin levels is not routinely performed in SSZ treated patients (22,23).

In our placebo-controlled study of SSZ in JCA low serum immunoglobulin levels appeared in 4 out of 35 SSZ treated patients, while none of the 34 placebo treated patients developed this abnormality (13). Though the incidence of dysimmunoglobulinemia was not significantly different in the two study groups ($P = 0.11$), the frequency of this adverse event in our study made us more aware of this possible complication and made us realize the possible need for guidelines in managing this particular problem. In order to achieve this we reviewed the medical records of 6 patients (5 of them took part in the study (13)) who all had low serum immunoglobulin levels either at the start (n = 1) or during SSZ (n = 5) treatment.

Patients. The characteristics, the clinical response to SSZ treatment, and the effects of SSZ treatment on serum immunoglobulin levels of all patients are described in the cases 1-6 and are summarized in Tables 1 and 2. Serum immunoglobulin levels are shown in Table 3. Measurement of serum Ig classes and IgG subclasses was performed by nephelometry (nephelometer BN100 analyzer, Behrin, Marburg, Germany). Rabbit antisera to human immuno-globulins (IgG, IgA and IgM), and sheep antisera to human IgG subclasses, and protein controls, were obtained from Dade Behring, (Marburg, Germany).

Patients 1, 2, 3, 4 and 6 took part in the published 24 weeks placebo-controlled SSZ treatment study in JCA (13). Case 5 started SSZ treatment just after the closure of inclusion of new study patients. In all the patients the SSZ treatment dose, 50 mg/kg/day, was gradually reached within one month. All patients had a follow-up of 4-6 years after starting SSZ treatment. Low serum immunoglobulin levels were defined as serum levels below 2 SD

Table 1. Characteristics of 6 patients with juvenile chronic arthritis (JCA) treated with sulfasalazine (SSZ)*

	Case 1	Case 2	Case 3	Case 4
Sex	Female	Female	Female	Female
JCA onset age (years)	8.2	1.6	1.8	1.5
Age at start SSZ (years)	9	4	5	7
Onset type JCA	poly	oligo	oligo	poly
Actual type JCA	poly	oligo (iridocyclitis)	oligo	poly
Antinuclear antibodies	negative	positive	negative	positive
IgM-RF	negative	negative	negative	negative
HLA-B27	positive	negative	negative	negative
JIA type (ILAR)	enthesitis related arthritis	persistent oligoarthritis	persistent oligoarthritis	polyarthritis RF negative
Disease duration before start SSZ (months)	9	24	38	77
Medication before SSZ	NSAID	NSAID, IAC	NSAID, IAC	NSAID, intramuscular gold

Table 2. Effects and actions taken in 6 patients with juvenile chronic arthritis (JCA) who showed changes in serum immunoglobulin levels*

	Case 1	Case 2	Case 3	Case 4
Effect SSZ on serum immunoglobulins	Low IgA * Low IgG2	Low IgA	Low IgA Low IgG Low IgM	Low IgA
Period of SSZ treatment†	3 months	3 months	3 months	18 months
Action taken upon change Ig-levels	Stop SSZ	Stop SSZ↓	Stop SSZ	SSZ continued
Follow-up serum immunoglobulins	Normal	Normal	Normal	Normal
Clinical response SSZ treatment	Unchanged	Temporary remission	Complete remission	Improved

of the mean value for healthy age matched controls (Central Laboratory Bloodtransfusion Services, Amsterdam, The Netherlands). Partial IgA deficiency was defined as serum IgA above 0.01 g/l but below 2 SD of the normal value for age. Dysimmunoglobulinemia was defined as a low level of one or more individual Ig classes while other Ig classes were within the normal range. Hypogamma-globulinemia was defined as all serum immunoglobulin levels (IgA, IgG, and IgM) below 2 SD of the normal value for age.

Case 1. This 9-year-old HLA-B27 positive girl with polyarthritis and a father with ankylosing spondylitis (ILAR / enthesitis related arthritis) (24) was treated with NSAIDs for 9 months before SSZ was added. She tolerated SSZ well but her polyarthritis persisted. Three months after starting SSZ treatment we found low levels of IgA (0.11 g/l) and IgG2 (0.30 g/l)(normal value 0.98-4.8 g/l). SSZ was stopped and methotrexate (MTX) was started. After 6 months of MTX treatment her arthritis resolved and the level of IgA (0.57 g/l) increased to an almost

	Case 5	Case 6 (first course)	Case 6 (second course)
	Female	Female	
	2	6.4	
	5	6	8
	poly	poly	poly
	poly	poly	poly
	negative	negative	negative
	negative	negative	negative
	not done	negative	negative
	polyarthritis RF negative	polyarthritis RF negative	polyarthritis RF negative
	36	5	29
	NSAID, IAC	NSAID	NSAID

Footnotes **Table 1.**
* Poly = polyarticular onset; oligo = oligoarticular onset; IgM-RF = IgM rheumatoid factor; ILAR = International League of Associations for Rheumatology (24); JIA = Juvenile Idiopathic Arthritis (24); IAC = intra-articular corticosteroids

	Case 5	Case 6 (first course)	Case 6 (second course)
	Low IgA	No effect	No effect
	6 months Dose SSZ ↓	6 months SSZ continued	2 years SSZ continued
	Normal Improved	Gradual increase IgA Improved	Gradual increase IgA: normal Improved

Footnotes **Table 2.**
* Low = below 2 SD of mean value for healthy age-matched controls;
† SSZ treatment dose of 50 mg/kg/day. In all cases SSZ treatment was discontinued at some point during follow-up irrespective of the effects of SSZ on serum immunoglobulin levels.

normal level, but the low IgG2 (0.38 g/l) level persisted. Three years later her IgA was 1.15 g/l and IgG2 1.06 g/l.

Case 2. This 4-year-old girl with a persistent oligoarthritis was treated for 2 years with several types of NSAIDs and intra-articular steroids. Three months after commencing SSZ treatment her arthritis resolved. All serum immunoglobulin levels declined, especially IgA (0.09 g/l). SSZ was stopped and IgG and IgM reached pre-treatment levels within 4 months. IgA attained a normal value 10 months after stopping SSZ treatment. Her arthritis recurred within 3 months after stopping SSZ. The following three years her arthritis was treated with NSAIDs and regular intra-articular steroid injections. Eleven months after stopping SSZ treatment she developed diabetes mellitus. IgA, IgG and IgM levels stayed within the normal range.

Case 3. This 5-year-old girl with a persistent oligoarthritis was treated for three years with NSAIDs and corticosteroid joint injections. Six weeks after beginning SSZ treatment her arthritis resolved. After 3 months of SSZ treatment she developed low IgA (0.09 g/l), low IgG (4.64 g/l), low IgG2 (0.51 g/l) (normal value 0.72-3.4 g/l) and low IgM (0.21 g/l) levels. During the SSZ treatment period she went through several mild upper respiratory tract infections that resolved spontaneously. Because of the low immunoglobulin levels SSZ treatment was stopped. IgG (5.42 g/l), IgG2 (0.92 g/l) and IgM (0.77 g/l) levels attained normal values within 3 months and the IgA (0.61 g/l) level showed a normal value after 14 months. Her arthritis remained in remission during the following 6 years. Three years after stopping SSZ treatment she spontaneously developed low IgA (0.24 g/l) and low IgG2 (0.56 g/l) levels which still persist two years later.

Case 4. This 7-year-old girl with polyarticular JCA (ILAR / RF negative polyarthritis) since the age of 18 months was treated for five years with several NSAIDs. Then intramuscular gold was added but despite 6 months of treatment her polyarthritis deteriorated further. The gold medication was replaced by SSZ. She had a good clinical response to SSZ. After 3 months of SSZ treatment a subnormal IgA (0.51 g/l) level developed. SSZ was continued in the same dose and her immunoglobulins were regularly checked. IgA remained at a stable subnormal level, and IgG and IgM stayed within the normal range. Eighteen months after starting SSZ a leukopenia occurred for which the SSZ dose was reduced to 25 mg/kg/day. Her arthritis was quiescent at that moment and the IgA level was 0.62 g/l. The number of leukocytes normalized, but gradually her polyarthritis became more active. SSZ was stopped and oral MTX 10 mg/m2 was started. The IgA rose to 1.26 g/l.

Case 5. This 5-year-old girl, known to have a polyarticular onset JCA (ILAR / RF negative polyarthritis) since the age of 2 years, was in remission for more than a year but then her disease flared up with an active polyarthritis. Treatment with NSAIDs was resumed and SSZ was added and the arthritis diminished. After 6 months of treatment a low IgA (0.12 g/l) level developed. The SSZ dose was reduced to 25 mg/kg/day after which the IgA (0.24 g/l) level slightly increased. The arthritis stayed quiescent for another 5 months but then a severe polyarthritis developed. SSZ was stopped and inflamed joints were treated with intra-articular steroids. Four months after SSZ discontinuation the IgA (0.69 g/l) level was normal.

Case 6. This 6-year-old girl had a polyarticular onset JCA (ILAR / RF negative polyarthritis) and a partial IgA-deficiency, which was attributed to a physiological maturational delay. After 6 months of NSAID treatment SSZ was added. She tolerated SSZ well and the arthritis diminished. During 6 months of SSZ treatment IgA (0.15 g/l), IgG (14.49 g/l) and IgM (1.44 g/l) levels remained relatively unchanged. After cessation of SSZ treatment the levels of all immunoglobulins increased. Her arthritis remained quiescent for some months but then recurred. SSZ was reintroduced and during this second period of SSZ treatment, IgA (0.58 g/l) levels increased to normal levels and IgM and IgG stayed within the normal range. She

Table 3. Serum immunoglobulin levels (g/l) before, during and after sulfasalazine (SSZ) treatment in 6 juvenile chronic arthritis (JCA) patients

Case	Before SSZ treatment		During SSZ treatment	After SSZ treatment†	Range of normal values‡
1	IgA	2.45	(+ 3 months) 0.11*	(+ 12 months) 0.57	0.54 - 2.5
	IgG+	14.88	16.44	9.83	5.20 - 14.3
	IgM	2.83	1.90	1.43	0.28 - 1.9
2	IgA	1.53	(+ 3 months) 0.09*	(+ 10 months) 0.75	0.55 - 2.2
	IgG+	13.93	9.29	15.20	5.20 - 13.4
	IgM	1.25	0.93	1.30	0.24 - 1.8
3	IgA	0.80	(+ 3 months) 0.09*	(+ 14 months) 0.59	0.55 - 2.2
	IgG+	8.30	4.64*	7.22	5.20 - 13.4
	IgM	0.90	0.21	1.19	0.24 - 1.8
4	IgA	1.64	(+ 3 months) 0.51*	(+ 24 months)§ 1.26	0.54 - 2.5
	IgG+	11.90	8.48	13.90	5.20 - 14.3
	IgM	0.98	0.53	0.82	0.28 - 1.9
5	IgA	0.65	(+ 6 months) 0.12*	(+ 4 months) 0.69	0.55 - 2.2
	IgG+	5.89	7.16	13.02	5.20 - 13.4
	IgM	0.71	0.68	1.48	0.24 - 1.8
6 first course¶	IgA	0.13*	(+ 6 months) 0.15*	(+ 13 months) 0.42*	0.54 - 2.5
	IgG+	16.32	14.49	16.49	5.20 - 14.3
	IgM	1.62	1.44	1.94	0.28 - 1.9
6 second course	IgA	0.42*	(+ 12 months) 0.58	(+ 2 months) 0.69	0.54 - 2.5
	IgG+	16.49	17.44	16.72	5.20 - 14.3
	IgM	1.94	1.14	1.32	0.28 - 1.9

† First occasion after discontinuation of SSZ treatment when IgA levels within the normal range were detected.
‡ Range of normal values of serum immunoglobulin levels (g/l) in age matched controls (Central Laboratory Bloodtransfusion Services, Amsterdam, The Netherlands). Ranges indicated are the 0.025-0.975 percentiles (2 SD).
IgG+ subclasses were determined in all cases: all patients had IgG subclass values within the normal range on all occasions except Case 1 and Case 3.
* Concentration of the indicated Ig class is below 2 SD of normal values for age.
§ Serum Ig levels shortly after discontinuation of SSZ are not known. IgA levels had already normalized during SSZ treatment;
¶ Case 6 started treatment with a low IgA concentration; she had two periods of SSZ treatment.

again reacted well to SSZ treatment and her arthritis resolved. Treatment was continued for another 2 years without any clinical or laboratory sign of adverse events. SSZ was stopped and her arthritis remained in remission.

DISCUSSION

Immunoglobulin levels, especially levels of IgA can be influenced by SSZ treatment in JCA as can be learned from these cases and the literature (9,13,17,18,20,21). The implication of this laboratory finding for treatment strategy is less clear. Transient hypogammaglobulinemia

(as in Case 3) or dysimmunoglobulinemia may develop (as in Case 1, 2, 4, and 5). Case 6 illustrates that a patient with a partial IgA deficiency at the start of SSZ treatment does not necessarily develop lower IgA levels during SSZ treatment. None of the studied patients who developed dysimmunoglobulinemia showed any clinical signs of immune deficiency, and the immunologic changes could only be detected by laboratory investigation.

The frequency of development of dysimmunoglobulinemia during SSZ treatment in adult RA patients is unknown but seems uncommon. Delamere and Farr describe 4 adult RA patients in case reports (20,21) and later Farr mentions a percentage of 1% of patients developing a hypogammaglobulinemia and 3% of patients developing low IgA levels (18). These percentages were based on studies in 350 adult RA patients. Other studies, which mention longitudinal evaluation of serum immunoglobulin levels, report a general decrease of immunoglobulin levels during SSZ treatment and development of hypogammaglobulinemia in only one other patient (3,17,19). Most studies on SSZ treatment in RA do not routinely evaluate levels of immunoglobulins (1,2,4,25); therefore cases of hypogammaglobulinemia or dysimmunoglobuline-mia may have remained undetected (22,23). The frequency of occurrence of dysimmunoglobulinemia or hypogammaglobulinemia in pediatric JCA patients treated with SSZ is also unknown. The measurement of immunoglobulins was reported in three studies: Ansell (open study SSZ: 51 patients) (7), Suschke (open study SSZ: 11 patients) (9) and Van Rossum (placebo-controlled, 35 patients SSZ) (13). Suschke mentioned a general decrease of immunoglobulin levels during treatment but not below normal values; Ansell did not report on any immunological abnormality, and we reported a general decrease of immunoglobulin levels in SSZ treated patients and 4 patients who showed dysimmunoglobulinemia. Two studies describe development of dysimmuno-globulinemia in pediatric inflammatory bowel disease (IBD) patients treated with SSZ. The condition persisted after cessation of therapy in some cases (26,27).

The mechanism by which dysimmunoglobulinemia develops during treatment with SSZ is not clear. In RA patients SSZ seems to affect lymphocyte function, decreasing the in vitro proliferative response to immunogenic stimuli (28). The in vitro activity of B cells measured as proliferation and immuno-globulin synthesis was inhibited by SSZ (29,30). In addition, SSZ has been shown to decrease serum levels of IL-6 in RA patients, whereas IL-6 is known as a potent B-cell growth and differentiation factor (19). It is suggested that SSZ inhibits IL-6 production and thereby downregulates B-cell differentiation and maturation (19). In patients with RA, SSZ treatment reduces γ/δ lymphocytes in the duodenal mucosa, which may indicate an effect of SSZ on the gut immune system. So far, studies on the effect of SSZ on the gut immune system have, however, not been conclusive (15,19,31). In our study a positive response to SSZ treatment coincided with the development of dysimmunoglobulinemia in Cases 2, 4 and 5, but not in Case 1. Our patient (Case 3) with hypogammaglobulinemia has been in complete remission for more than 5 years. A recurrence of normal immunoglobulin levels does not always coincide with a relapse of disease as is demonstrated in Case 3 (32). It is also suggested that a genetic predisposition may explain selective IgA deficiency in patients treated with SSZ (18,20,27), but no conclusive studies have yet been published.

Selective IgA deficiency is frequently associated with autoimmune phenomena and with JCA (33). Low IgA levels are rather frequent (2-4%) among JCA patients independent of drug therapy (32,34). One study reported fluctuation of IgA serum levels from deficient to normal during the course of JCA with and without the interaction of antirheumatic drugs (32). Several abnormalities in cellular and humoral immunity are described in JCA patients (35,36). It is suggested that drugs like SSZ induce "common variable" immunodeficiency in patients who have genetic predisposing factors for this disease (37). The spontaneous development of dysimmunoglobulinemia in our case 3 three years after SSZ and the development of diabetes mellitus in patient case 2 eleven months after SSZ, support the suggestion that certain patients are prone to develop more autoimmune phenomena. This observation merits further investigation. As is illustrated in case 6, a partial IgA deficiency (which was considered to be a physiologic maturational delay) can remain unchanged and even disappear during SSZ treatment with improvement of arthritis. Low IgA levels do not seem to be a contraindication to start SSZ therapy.

To our knowledge none of the pediatric patients described either in our case reports or in the literature with the occurrence of dysimmunoglobulinemia or hypogammaglobulinemia during SSZ treatment, has developed serious problems with infections (27,32). It is not known how many patients also had low IgG2 levels since this was only reported in one other patient (27). Deficiency of this IgG2 immunoglobulin subclass has been associated with a defective response to polysaccharide antigens and with an increased incidence of infection in pediatric patients (38,39).

The question of whether one would have to stop treatment with SSZ when a dysimmunoglobulinemia or hypogammaglobulinemia develops remains unanswered with this study. In our opinion these immune abnormalities merit surveillance. We suggest monitoring immunoglobulin levels every 3 months during the first year after starting SSZ treatment and yearly thereafter. If hypogammaglobulinemia develops we suggest stopping SSZ treatment; if a dysimmunoglobulinemia develops we suggest continuing SSZ treatment unchanged and closely monitoring the development of clinical symptoms and development of other immune abnormalities every 3 months. In the situation where a combination of low IgA and low IgG2 levels occurs, we recommend the same close monitoring and only stopping SSZ treatment when either one of these immunoglobulins can no longer be detected. If a complete IgA deficiency develops treatment should be stopped.

As long as the mode of action by which SSZ affects the immune system and reduces immunoglobulin levels is not elucidated, meticulous clinical and laboratory follow-up is needed to prevent patients from developing potentially health threatening adverse events.

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Chapter 4

Anti-cyclic citrullinated peptide (Anti-CCP) antibodies in children with juvenile idiopathic arthritis

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ABSTRACT

Objective. To determine if anti-cyclic citrullinated peptide antibodies (anti-CCP) can be detected in sera of patients with juvenile idiopathic arthritis (JIA) and if they can be used to identify patients with a more destructive course of disease.

Methods. One hundred serum samples of 71 patients with JIA taken at different time points in their disease course were analyzed by a commercially available anti-CCP ELISA. Follow-up serum samples from 28 patients were also tested. Correlations between anti-CCP and disease characteristics, medication, and radiological damage (presence of joint space narrowing and/or erosions) were also determined.

Results. The serum samples came from patients of all 8 different subtypes of JIA (mean age: 9.6 years, median: 10.5; disease duration mean: 39 months, median: 24) including 11 polyarticular rheumatoid factor positive (IgM-RF) patients. Anti-CCP was positive in 73% of the IgM-RF positive JIA patients and in 3% of the other JIA patients ($P < 0.0001$). Disease duration, medication, and antinuclear antibody positivity did not differ significantly between anti-CCP positive and negative patients. Testing of follow-up samples showed almost identical anti-CCP results. All IgM-RF positive JIA patients had radiological damage ($P < 0.001$). Of the anti-CCP positive patients, 80% had radiological damage resulting in a significant difference between anti-CCP positive and negative patients ($P = 0.009$) with an odds ratio (OR) of 12.7, but corrected for IgM-RF, the OR was no longer significant ($P = 0.88$).

Conclusion. Anti-CCP antibodies can be detected in sera of patients with JIA but almost exclusively in the subset of patients with polyarticular IgM-RF.

INTRODUCTION

Juvenile idiopathic arthritis (JIA, previously juvenile chronic arthritis) is a clinically heterogeneous group of arthritides occurring in children younger than 16 years with an onset characterized primarily by arthritis persisting for at least 6 weeks and without a known cause (1,2). The diagnosis of JIA is made clinically after exclusion of infections or other inflammatory diseases. The serological support is limited to the determination of antinuclear antibodies (ANA) and rheumatoid factor (IgM-RF). ANA are present in 75-85% of children with oligoarticular JIA and in 40-50% of children with polyarticular JIA. ANA are unusual in patients with systemic JIA. A relation between the presence of ANA in the serum of JIA patients and the occurrence of uveitis has been described but their presence is not related to the disease course nor to the severity of the joint involvement (3). IgM-RF is present in 5-10% of JIA patients and the clinical pattern of these patients is very similar to rheumatoid arthritis (RA) in adults (4-6).

RA is the most common chronic inflammatory disease of joints in adults (1-3% of the population) and this diagnosis also depends primarily on clinical manifestations. IgM-RF can be detected in about 75% of RA patients but its specificity is limited (7). Recently, Schellekens and coworkers described a serological test, the anti-cyclic citrullinated peptide (anti-CCP) ELISA, that is very specific (96-98%) for RA with a sensitivity of more than 60% (8). Anti-CCP auto-antibodies have been shown to be present in 60-75% of established RA patients (9-11). The probability of diagnosing RA correctly at an early stage of disease can be significantly increased by testing both IgM-RF and anti-CCP (10,12). Other studies have shown that anti-CCP positive RA patients developed more severe radiological damage than anti-CCP negative RA patients after 3-6 years of follow-up (11,13).

The aim of the present study was to determine if anti-CCP can be detected in sera of JIA patients to support the diagnosis and if anti-CCP can be used to identify JIA patients with a more severe destructive course of the disease.

MATERIALS AND METHODS

Sample collection. Serum samples of 71 JIA patients who consecutively visited the departments of (pediatric) rheumatology in Leiden and Amsterdam were analyzed. Informed consent was obtained according to the medical ethical regulations. Two or more sera taken at different time points in the disease course (before change of medication) were available from 28 of the 71 patients to determine if the anti-CCP ELISA converted from positive to negative or vice versa during follow-up. In total 100 serum samples were tested. All patients were classified according to the ILAR criteria (2). Data concerning clinical signs of disease (clinical arthritis defined as swelling and/or pain with limitation of motion, fever, rash, visceral involvement), medication use, laboratory variables (IgM-RF, ANA), and radiological joint damage (defined as the presence of joint space narrowing and/or erosions), were collected from the patient files. The radiological data collected were roughly from the same time point as serum collection.

Measurements. IgM-RF was measured by ELISA as described previously (14). ANA was assayed by a standard indirect immunofluorescence technique on ethanol fixed HEp-2 cells (Biomedical Diagnostics, Brugge, Belgium). ANA serum titers at ≥1/40 were considered positive. IgM-RF and ANA were determined at disease onset. Anti-CCP antibodies were tested by a commercially available ELISA kit purchased from Euro-Diagnostica b.v. (Arnhem, The Netherlands) containing the cyclic citrullinated peptide cfc1-cyc as described by Schellekens, et al (10). For the determination of anti-CCP in the sera the cut-off value chosen was 60 units rather than the 50 units recommended by the kit. In our cohort sera, the cut-off of 60 units seemed to guarantee the highest specificity without significant loss of sensitivity as is illustrated in Figure 1. All sera were analyzed at least in duplicate, and the results were averaged. A serum control was included on all plates to monitor plate-to-plate variation. Variation never exceeded 5%, and values were therefore not corrected.

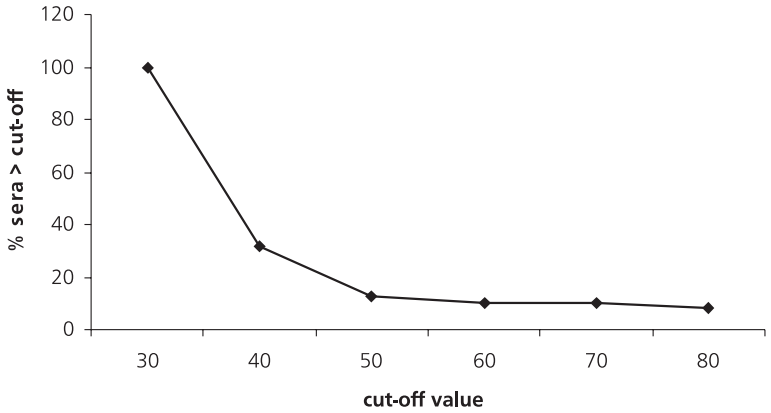

Figure 1. Relationship between the cut-off value of anti-CCP ELISA and the percentage of sera of JIA patients with values above the cut-off. X-axis: values of anti-CCP ELISA (units) (Euro-Diagnostica b.v., Arnhem, The Netherlands). Y-axis: percentage of sera of JIA patients with values above cut-off.

Statistical analysis. Statistical analyses were performed using SPSS software. The Fisher's exact test and Student's t-test were used for testing the significance of differences in variables between anti-CCP positive and anti-CCP negative patients. The associations between anti-CCP measurements, disease activity, and radiological data were evaluated with random effects logistic regression to account for the repeated anti-CCP measurements in some of the patients. A P-value of ≤ 0.05 was considered statistically significant.

RESULTS

One hundred sera from 71 JIA patients at different time points in their disease course were analyzed. Patient and disease characteristics at the time of serum collection are shown in Table 1. The 100 sera belonged to 71 JIA patients (age 2-20 years, mean 9.6 years (SD 4.5),

Table 1. Patient and disease characteristics of 71 juvenile idiopathic arthritis (JIA) patients at the time point of serum collection.

JIA subtype	Patients, n	Tested sera*, n	Disease duration months**, mean (range)	DMARD use at time point of serum collection***, n	Clinical arthritis present at time point of serum collection†, n	Radiological damage present‡ (no data available), n
Systemic arthritis	10	18	60 (3-141)	10	13	10 (1)
Persistent oligoarthritis	11	13	33 (3-134)	1	8	5 (4)
Extended oligoarthritis	6	11	53 (3-223)	4	8	0 (1)
IgM-RF negative polyarthritis	24	35	26 (3-71)	20	25	14 (1)
IgM-RF positive polyarthritis	11	12	26 (6-245)	5	12	11 (1)
Psoriatic arthritis	3	3	45 (36-65)	2	2	1
Enthesitis related arthritis	2	2	6 (3-12)	1	1	1
Other arthritis	4	6	67 (15-122)	5	4	1

* 28 patients had more than one serum sample tested at different time points in their disease course;
** The disease duration calculated at the time point of serum collection;
*** DMARD included sulfasalazine, hydroxychloroquine, methotrexate, etanercept;
† Clinical arthritis defined as swelling and/or pain with limitation of motion;
‡ Radiological damage defined as erosions and/or joint space narrowing (at the time point of serum collection).
Other arthritis is defined as not fulfilling one category within the JIA definition (2).

median 10.5 years) of all 8 different JIA subtypes. One or more follow-up sera were available from 28 patients randomly distributed over the different JIA subtypes. The interval between the tested serum samples of one patient ranged between 1 and 84 months (mean 26 ± 20 months, median 23).

The disease duration had a mean of 39 ± 47 months (median 24 months, and range 3-245). Seventy-seven percent of the patients had clinical arthritis at the time of serum collection. Radiological data were available for 66 of the 71 patients.

Anti-CCP test results. Ten JIA patients (15%) tested anti-CCP positive and 8 of these anti-CCP positive JIA patients were also IgM-RF positive. A positive anti-CCP test occurred significantly more often in polyarticular IgM-RF positive patients compared to the other JIA subtypes ($P < 0.0001$). The occurrence of anti-CCP among the other subtypes of JIA ($P = 0.17$) was rare as is shown in Table 2. Of the 11 IgM-RF positive patients, 8 (73%) had a positive anti-CCP test with values ranging between 60 and 1915 units. One JIA patient with persistent oligoarthritis had a clearly positive anti-CCP test (674 units), while one JIA patient with other arthritis (extended oligoarthritis with a second degree relative with psoriasis) gave different results at the 2 occasions that serum was collected. This patient was first tested anti-CCP positive (77 units) but the serum collected 2 years later was anti-CCP negative. This was the one and only patient who had different anti-CCP results when tested at more than one occasion.

Clinical correlation. Disease duration did not differ significantly between anti-CCP positive and anti-CCP negative patients ($P = 0.34$).

Table 2. Results of anti-CCP ELISA using cfc1-cfc peptide in sera of 71 JIA patients.

JIA type	Patients, n	Anti-CCP positive, n	Value ELISA, units Range	Anti-CCP negative, n	Value ELISA, units Range
Systemic arthritis	10	-		10	30-52
Persistent oligoarthritis	11	1	674	10	33-47
Extended oligoarthritis	6	-		6	35-47
IgM-RF negative polyarthritis	24	-		24	32-51
IgM-RF positive polyarthritis	11	8	60-1915		36-47
Psoriatic arthritis	3	-		3	32-37
Enthesitis related arthritis	2	-		2	37-50
Other arthritis	4	1*	77	3	34-38

Anti-CCP positive: values ≥ 60 units; Anti-CCP negative: values ≤ 59 units.

* One patient was tested with different results: at disease duration of 8 years: anti-CCP positive (77 units); 24 months later the results were: anti-CCP negative (35 units)

All anti-CCP positive patients had clinical arthritis at the time of serum collection, as was the case in only 39 of 61 (64%) anti-CCP negative patients ($P = 0.025$). There was no significant difference in the use of disease modifying antirheumatic drugs between anti-CCP positive and negative patients in this study.

Radiological damage was observed on the radiographs of 30/66 (46%) of the evaluable patients: 8/30 (27%) of the patients with radiological damage were anti-CCP positive, and 11/30 (37%) were IgM-RF positive. All 11 IgM-RF positive JIA patients had radiological damage ($P < 0.001$) compared to 8 out of 10 anti-CCP positive patients ($P = 0.009$). The 2 positive anti-CCP patients without IgM-RF had no radiological abnormalities. Radiological damage occurred significantly more in the anti-CCP positive patients than in the anti-CCP negative patients ($P = 0.009$) with an odds ratio (OR) of 12.7 (95% confidence interval 1.5-108), but when corrected for IgM-RF status the OR was no longer significant ($P = 0.88$).

DISCUSSION

The anti-CCP ELISA is a new diagnostic test with extremely high specificity for RA (8). We investigated whether anti-CCP antibodies could also support the diagnosis of JIA. We did not test sera from healthy children or those with infections or other autoimmune diseases since such analyses have been performed extensively in adults (8,10,15). The high prevalence of anti-CCP in polyarticular IgM-RF positive JIA patients shows that anti-CCP selects for a specific subgroup of JIA patients but is not supportive for the diagnosis of JIA in general.

The anti-CCP test originates from the detection of other autoantibodies commonly seen in RA: antiperinuclear factor (APF) and anti-keratin antibodies (AKA). Schellekens, et al. have shown that APF and AKA specifically bind to substrates containing the modified amino acid citrulline (9). The methodological difficulties in the assessment of APF and AKA are summarized by Van Boekel, et al. (8) and the anti-CCP assay might be looked at as a simple,

more specific, and functional replacement of the immunofluorescence tests used for the detection of APF and AKA.

Published studies have reported substantial differences of occurrence of APF and AKA in patient populations with JIA; results varied from 1% to 37% for APF (16,17) and 2% to 50% for AKA (18,19). These discrepancies were attributed to either methodological differences in the detection of the autoantibodies or differences in the JIA population studied. Several authors have noted that APF or AKA were most frequently detected in the subgroup of IgM-RF positive JIA patients (17-21). These observations are in agreement with our results of predominance of occurrence of anti-CCP in this subgroup.

In the literature, reports of anti-CCP ELISA in JIA are very scarce. Bizzaro, et al. (15) describe negative anti-CCP results in 3 tested JIA patients (subtype unknown). Recently, Avcin, et al. (22) described anti-CCP positivity in 2 out of 108 tested JIA patients (oligoarticular and polyarticular IgM-RF negative patients). One polyarticular IgM-RF positive JIA patient tested negative. Although their cut-off value, using the same commercial anti-CCP test we used, was 70 units, our results were very similar. In our study only one patient with a value of 60 units (Table 2) was considered anti-CCP positive, while all others had values above 70 units. Therefore our results are in agreement with the results published by Avcin and coworkers (22) and indicate that anti-CCP antibodies are present in only a subset of JIA patients.

Because of the very high specificity of this autoantibody system for adult RA (more than 97%) (8), it seems likely that this subset includes JIA patients who are developing a pattern of involvement like that of adult RA. The observation that the titer values in the anti-CCP positive JIA patients generally were lower than those observed in adults with RA is in line with this assumption of a developing disease. Longer follow-up of this group of JIA patients will provide a definite answer whether anti-CCP antibodies can predict the development of an adult RA-like disease pattern in JIA.

It is known that IgM-RF positive JIA often has a disease course similar to RA in adults (6). Our study confirms this similarity.

Although a role for anti-CCP in RA has been suggested, the significance of anti-CCP in the disease pathogenesis remains unclear (23). All IgM-RF positive JIA patients had clinical arthritis and radiological damage, and almost all were anti-CCP positive. These results confirm previous studies in adult early RA that both IgM-RF and anti-CCP antibodies can predict the development of a more severe destructive disease course (11-13) and that their simultaneous presence may be an indication for earlier immunosuppressive treatment (24).

We have shown that anti-CCP antibodies can be found incidentally in the serum of children with several subtypes of JIA, but that they are commonly present in polyarticular IgM-RF positive JIA patients. Further follow-up studies will more firmly establish whether the presence of anti-CCP antibodies in JIA patients predicts the development of a disease course like adult RA and selects JIA patients with a more severe destructive disease course.

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Chapter 5

Radiologic features in juvenile idiopathic arthritis: a first step in the development of a standardized assessment method

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ABSTRACT

Objective. To describe radiologic features of patients with juvenile idiopathic arthritis (JIA) in a standardized manner, to test the reliability and feasibility of this description, and to correlate these features with clinical signs as a first step in the development of a standardized assessment method.

Methods. The placebo-controlled study of sulfasalazine in patients with oligoarticular, extended oligoarticular, and polyarticular JIA performed by the Dutch Juvenile Idiopathic Arthritis Study Group yielded the data for this study. All trial entry radiographs (clinically involved joints and contralateral joints) were scored (in consensus by a skeletal radiologist and pediatric rheumatologist) for the presence of swelling, osteopenia, joint space narrowing, growth abnormalities, subchondral bone cysts, erosions and malalignment.

Results. Data on 67 of 69 patients were analyzed. The mean age was 9.1 years (range 2.5-17.6 years), and the median disease duration was 24 months (range 5-176 months). Thirteen percent of the patients were IgM rheumatoid factor (IgM-RF) positive, and 16% were HLA-B27 positive. All 68 clinically evaluated joints were included in the maximum of 19 radiographed joints (or joint groups) per patient. The mean number of radiographed joints per patient was 7 (range 2-15); knees, hands, ankles and feet were most frequently affected. Fifty-eight patients (87%) had radiologic abnormalities in at least one joint (soft-tissue swelling in 63% of patients, growth disturbances in 48%, joints space narrowing in 28%, and erosions 15%). In total, half of the radiographs of the clinically involved joints showed radiologic abnormalities, including two-thirds of the radiographs of the clinically affected hands and knees. Univariate analysis revealed a good correlation between the overall articular (clinical) severity and the presence of radiologic abnormalities (odds ratio [OR] 1.38, $P < 0.0001$). Multivariate analysis showed increased ORs for the presence of radiologic abnormalities and IgM-RF positivity (OR 4.6, $P = 0.005$) or HLA-B27 positivity (OR 3.0, $P = 0.004$). In general, reproducibility of the radiologic scoring method was good (kappa-coefficient of 0.74 [range 0.40-0.86]), although there were scoring discrepancies for swelling, osteopenia and growth disturbances. The scoring took 10-20 minutes per patient.

Conclusions. Our model of describing and scoring radiologic abnormalities of radiographed joints in JIA was feasible, mostly reproducible, correlated well with the overall articular severity score, and added substantial new information not available on clinical examination.

INTRODUCTION

Juvenile idiopathic arthritis (JIA; previously called juvenile chronic arthritis [JCA] (1) can lead to destructive lesions of joint cartilage and periarticular bone. As in adult rheumatoid arthritis (RA), radiographs are deemed important to document this damage and are used widely by clinicians to assess disease severity and progression. The extent of reported radiologic damage varies with the type of JIA patients studied and the definition of radiologic damage. In recent long-term outcome studies of patients with oligoarticular-onset and polyarticular-onset JIA, joint damage in up to 70% of patients was observed (2,3).

Compared with RA, the radiologic manifestations of JIA differ with regard to 1) the number and distribution of involved joints (e.g., in oligoarticular JIA, fewer than 5 joints are involved, usually asymmetrically; the most frequently involved joints are the knee, ankle, elbow and hand); 2) the manifestation of joint space narrowing (articular cartilage is generally thicker in children than in adults, and radiographic narrowing of a joint space is the reflection of cartilage loss) (4); 3) the development of growth disturbances in JIA (inflammation occurs in a developing joint); 4) joint ankylosis (joint ankylosis occurs more promptly in children than in adults, particularly in the carpal and tarsal joints and in the cervical spine) (5); and 5) joint erosions, which develop later in the disease course in JIA (6-10). Thus, although radiologic scoring systems are most advanced in RA, any scoring system in JIA modeled on this experience must take these unique features of JIA into account.

Pettersson and Rydholm made the first attempt to develop an objective radiologic scoring system for joint abnormalities of the large joints in JIA (11,12). Later, carpal length measured by plain-film radiography (specifically, the ratio of the carpal length to the length of the second metacarpal) was introduced as radiologic assessment for cartilage integrity (13,14). Both techniques have their limitations in use, since they are not applicable to all of the possibly involved joints in JIA.

A series of radiographs comprise the simplest and cheapest permanent record of the cumulative joint damage caused by the disease. Other methods of imaging, such as magnetic resonance imaging and ultrasonography, may offer unique, useful features (15,16), but are unlikely to replace plain radiography as the standard for some time to come (17,18). Because JIA therapy is moving toward early treatment with potentially toxic second-line antirheumatic drugs, there is a growing need for a clear and reproducible radiologic assessment standard, both to select and to evaluate patients. The aim of our study was to make a first step in the development of a standardized assessment method applicable to radiographs of patients with JIA, and to assess the reliability, feasibility and measurement properties of this method. The sensitivity to change and other methodologic issues of evaluation will be addressed in future studies.

The issues that we aimed to explore in this radiologic study were as follows: 1) assessment of the presence or absence of a comprehensive spectrum of radiologic features among JIA patients who took part in the sulfasalazine (SSZ) placebo-controlled study performed in the Netherlands (19), 2) testing of the reliability and feasibility of this assessment, and 3) evaluation of the correlation between these radiologic features and clinical signs.

PATIENTS AND METHODS

Cohort. The placebo-controlled SSZ study performed by the Dutch Juvenile Idiopathic Arthritis Study Group (19) yielded the data for the present study. Data on patients who had a complete clinical and laboratory assessment with a complete set of radiographs at study entry were included. All patients included in the original study fulfilled the European League Against Rheumatism criteria (20) for oligoarticular- or polyarticular-onset JCA and were between the ages of 2 years and 18 years, with onset of arthritis before the age of 16 years. For the purpose of the present study, patients were retrospectively reclassified according to the JIA subtypes.

Clinical data. In every patient, 68 joints were scored for swelling (range 0 - 3), pain on motion and/or tenderness (range 0 - 3), and limitation of motion (LOM) (range 0 - 4) (19). The overall articular severity score was defined as the sum of all scores for swelling, tenderness/pain, and LOM (range 0 - 10) (21). In this trial "clinical arthritis" was defined as the presence of swelling or LOM, in addition to either pain upon movement or tenderness. In the present study, joints with either swelling, pain or LOM (i.e. overall articular severity score ≥ 1) are described as joints with "clinical signs of disease" and include joints with clinical arthritis. For this radiologic study, we used all data on the radiographed joints/joint groups (maximum of 19 joints/joint groups per patient).

Radiologic data. *Collection of radiographs.* At entry into the SSZ/placebo trial, conventional film-screen radiographs of all affected joints (either tender, painful, swollen or limited in motion as judged by the treating physician) and the contralateral joints were obtained; these radiographs were used in the present study. Information about the duration of disease in the radiographed joint was not systematically collected. Although follow-up films were made in the trial, this report is limited to the baseline radiographs.

Reading method. After completion of the SSZ/placebo trial, the radiographs were read in chronologic order in a single session by a skeletal radiologist (PFD) and a pediatric rheumatologist (MAJvR) in consensus. The readers were unaware of the subtype of JIA and the clinical condition of the patient. All primary analyses were based on this first reading. To get an impression of reproducibility, the same readers reviewed a convenience sample (from the Leiden and Amsterdam centers) of these same radiographs 4 years later, with the same objective in an identical manner. The second scoring took place without knowledge of the results of the first scoring. Finally, the readers revised all radiograph findings that had discrepant scores between the first and second session, but now with the knowledge of both scores.

Joints scored. The following 19 joints/joint groups were evaluated by radiography: cervical spine (1 joint), 2 mandibles, 2 shoulders, 2 elbows, 2 hands (each hand comprises a joint group that includes all finger, metacarpal and wrist joints), 2 sacroiliac joints, 2 hips, 2 knees, 2 ankles and 2 feet (each foot comprises a joint group that includes all tarsal, metatarsal and

toe joints). In this report the term "joint" will be used for both a large single joint or a group of smaller joints (e.g., hands).

Features scored. A scoring list applicable to these 19 joints/joint groups was composed. The following features (collectively called radiologic abnormality) were scored: soft-tissue swelling, osteopenia, joint space narrowing, enlargement or other growth disturbances, subchondral bone cysts, erosions and joint position or alignment. A combination of radiologic joint scores for RA served as inspiration for the scoring of soft-tissue swelling, grading of erosions and joint alignment (22,23).

High-intensity light was used to assess soft-tissue swelling, and this was scored as present if a reflection of soft-tissue swelling was found around a joint. Subchondral osteoporosis was defined as present when a localized decrease of bone density was noticed around a joint. Growth abnormalities were analyzed with regard to the shape, development, and maturation of the bone (24,25). Overgrowth of the epiphyses was assessed by measurement of the epiphyses and compared with the contralateral side (26). Special attention was paid to acceleration of epiphyseal maturation, premature fusion of epiphysis (eventually resulting in an abnormally short bone), tapering of the juxta-epiphyseal parts of the shaft of the bone, deformity of the joint due to asymmetric growth, modeling abnormalities (e.g., "ballooned" epiphysis, squared patella, abnormal shape of carpal bones) (10). Joint morphology was assessed with reference to age- and sex-adjusted standards (27). If any of the above-mentioned growth abnormalities occurred, the joint/joint group was scored positive for growth abnormalities.

Subchondral bone cysts were defined as localized areas of bone destruction and scored positive when present around a joint. Erosions were defined as a discrete interruption of the cortical surface of the bone. Erosions were scored as absent or present, and graded according to the amount of destruction of the joint surface (DJS): DJS <25%, DJS 26-50%, DJS 51-75% and DJS >75% (22). In the present study results of grading of the DJS are not reported. In the assessment of joint alignment, abnormal joint position was defined as flexion deformity, (e.g., proximal interphalangeal joints, hands), subluxation (e.g., boutonnière deformity) or dislocation (e.g., ulnar and radial deviation). One joint/joint group could have a positive score for more than one feature, but each feature was counted only once (e.g., one joint/joint group could show more than one erosion, but the erosion score remained 1).

Index joint. An index joint can be described as a joint (or combination of joints) that represents the damage in all of the joints (i.e., the presence and extent of damage in this joint is highly correlated with the damage in the other joints of a patient). We investigated whether hand, foot or knee joints could be used as an index joint in JIA.

Laboratory data. The laboratory data at study entry included the erythrocyte sedimentation rate, as well as positivity for antinuclear antibodies (ANA), IgM and IgA rheumatoid factor (IgM-RF and IgA-RF, respectively), and HLA-B27.

Statistical analysis. The presence of radiologic abnormalities was summarized both at the level of the various joints and at the level of the patient. Standard and logistic regression models that included a random patient effect analyzed the association between different types of radiologic abnormalities, and between the presence/absence of radiologic abnormalities in the various joints and the characteristics of the patients. *P* values of less than or equal to 0.05 were considered significant. Cohen's kappa coefficient quantified the agreement between observer scores (28).

RESULTS

Patient characteristics. The placebo-controlled SSZ study included 69 patients with JIA. For the present study, 2 male patients were excluded: 1 was reclassified as having systemic JIA, and 1 had missing radiographs. Onset of JIA was oligoarticular in 37 patients and polyarticular in 30 patients (Table 1). The underlying diseases, using the JIA criteria (1) were as follows: persistent oligoarthritis (19 patients [28%]), extended oligoarthritis (8 [12%]), IgM-RF-negative polyarthritis (19 [28%]), IgM-RF-positive polyarthritis (9 [13%]), enthesitis related arthritis (7 [10%]), arthritis and psoriasis (1 [1%]), and other arthritis (4 [6%]). In each patient, a mean of 12.8 joints (range 1-68) showed clinical signs of disease, and of these joints, a mean of 5.0 (range 1-42) fulfilled the definition of clinical arthritis (Table 2).

Table 1. Characteristics at study entry of 67 patients with juvenile idiopathic arthritis (JIA) who participated in the placebo-controlled trial of sulfasalazine and whose radiographs were used for radiologic scoring evaluation*

Characteristic	Value
Age, mean (SD) years [range]	9.1 (4.1) [2.5-17.6]
Female	46 (69)
Disease onset before age 6 years	35 (52)
Disease onset at age 6-10 years	16 (24)
Disease onset beyond age 10 years	16 (24)
Disease duration, median (IQR) months [range]	24 (10-40) [5-176]
Polyarticular-onset type JIA	30 (45)
Oligoarticular-onset type JIA	37 (55)
>4 joints with clinical arthritis at study entry†	41 (61)
Antinuclear antibodies present	33 (49)
IgM rheumatoid factor present	9 (13)
HLA-B27 positive	11 (16)
Local corticosteroid use ever	30 (45)
DMARD medication use ever	5 (7)
Systemic corticosteroid use ever	2 (3)

* Except where otherwise indicated, values are the no. (%) of patients. IQR = interquartile range; DMARD = disease-modifying antirheumatic drug.
† Clinical arthritis defined as the presence of swelling or limitation of motion, plus pain upon movement or tenderness; total no. includes 12 patients with oligoarticular-onset JIA and a polyarticular disease course, and 1 patient with polyarticular-onset JIA with <5 joints with clinical arthritis at study entry.

Table 2. Per patient distribution of clinical signs and radiologic abnormalities in the radiographed joints*

	Number of joints with clinical signs or radiologic abnormality		Number of radiographed joints	
Variable	Mean	Range	Mean	Range
Clinical sign†				
Swelling	8.4	0-44	3.7	0-10
Pain	6.2	0-42	2.3	0-14
Limitation of motion	7.0	0-61	3.7	0-17
Clinical signs of disease‡	12.8	1-68	5.9	1-17
Clinical arthritis§	5.0	1-42	2.5	0-14
Radiologic abnormality¶				
All scored features	2.8	0-11	7.0	2-15
All scored features excluding soft- tissue swelling	2.3	0-9	7.0	2-15

* The term "joints" is used to describe either a single joint (e.g., metacarpal joint or knee joint) or a group of smaller joints (e.g., cervical spine, wrist).
† From among a total of 68 clinically evaluated joints/joint groups.
‡ Defined as joints with either swelling, pain, or limitation of motion, but not satisfying the definition of clinical arthritis.
§ Defined as joints with swelling or limitation of motion, plus pain upon movement or tenderness.
¶ From among a maximum of 19 radiographed joints/joint groups per patient.

Radiologically evaluated joints. Radiographs had been obtained for 94% of the swollen joints, 81% of the painful joints, 83% of the joints with limitation of motion and 85% of the joints with clinical arthritis. In total, 471 joints/joint groups were radiographed. The mean number of radiographed joints/joint groups per patient was 7 (range 2-15), and of these radiographed joints/joint groups, a mean of 5.9 (range 1-17) had clinical signs of disease in at least one of the joints of the joint group, and a mean of 2.5 (range 0-14) had clinical arthritis. Per patient, a mean of 2.8 (range 0-11) radiographed joints/joint groups showed radiologic abnormalities (Table 2).

Radiologic findings. Fifty-eight patients (87%) had radiologic abnormalities in at least one of their radiographed joints. The most frequent abnormality was soft-tissue swelling (63% of the patients), followed by growth disturbances (48%), joint space narrowing (28%) and erosions (15%) (Figure 1). With regard to the distribution of abnormalities among the radiographed joints, soft-tissue swelling was seen in 19% of the radiographed joints, followed by growth disturbances (11%), joint space narrowing (8%) and erosions (6%) (Figure 1). The most diverse radiologic signs of disease were noted in the hand, as well as in the knee, ankle and foot. Erosions were detected in one knee, while all other erosions were scored in the hand or the foot. The correlations between different radiologic features were modest (range r = 0-0.30), except for the relation between osteopenia and abnormal joint position (r = 0.51).
An index joint could not be identified. Of the 67 patients, 49 had either hand or foot radiographs. Of the 41 patients with hand radiographs, 22 showed radiologic abnormalities in the hands, together with radiologic abnormalities in other joint groups; of the remaining

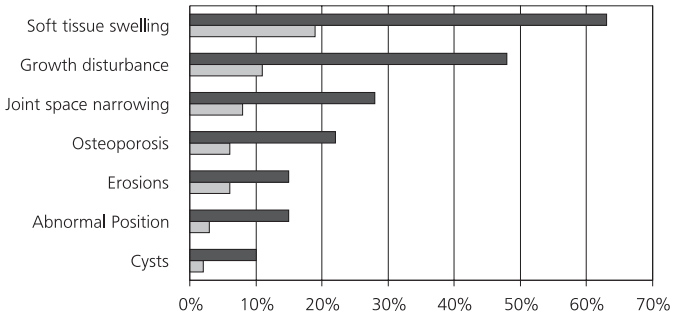

Figure 1. Proportion of patients with juvenile idiopathic arthritis showing a specific radiologic abnormality in at least one of their radiographed joints/ joint groups (solid bar), and proportion of joints/joint groups showing the specific radiologic abnormality (gray shaded bar). Note that one patient or one joint/joint group can have more than one abnormality.

19 patients with hand radiographs, 17 had no radiologic abnormalities in the hands despite having abnormalities in other joints, and 2 patients had radiologic abnormalities in only the hands. Exclusion of the radiologic sign of soft-tissue swelling from the analysis did not substantially alter the findings. Similarly, neither the foot, the knee, nor a combination of hand, foot and knee qualified to serve as an index of radiologic damage in the other joints (data not shown).

Association of radiologic findings and clinical signs. In 82% of radiologically swollen joints, clinical swelling coincided with the radiologic swelling in at least one of the joints of the joint group. In 92% of joints with joint space narrowing, clinical signs of disease were present in at least one of the joints of the joint group. Moreover, clinical signs of disease were present in 84% of joints with growth abnormalities and 65% of joints showing erosions. All cases of radiologically abnormal joint position showed clinical signs of disease.

Table 3. Clinical and radiologic abnormalities in 471 radiographed joints (joint groups) in 67 patients with juvenile idiopathic arthritis

	Total radiographed joint groups (n=471)		Joint groups with clinical arthritis (n=186)	
Joint site*	Total no. radiographs	% abnormal	No. radiographs	% abnormal
Knee	104	47	42	64
Ankle	84	27	35	31
Foot	70	36	20	45
Hand	86	57	55	66
Elbow	42	17	18	33
Shoulder	30	3	5	0
Hip	28	18	6	17
Cervical Spine	18	6	3	0
Sacroiliac joint	6	67	2	100
Mandible	3†	0	0	0
Total	471	35	186	50

* Total number of sites: maximum 19 joints/joint groups per patient (i.e., cervical spine, knee left, knee right etc.).
† Except for missing data on one right mandible, all joints (joint groups) were radiographed at both sides.

As noted before, 85% of joints with clinical arthritis were radiographed, and half of these radiographed joints showed abnormalities (Tables 3 and 4). Radiographs of the clinically affected hands and knees most frequently showed detectable radiologic abnormalities (66% and 64%, respectively). Of note, a relatively high proportion of hand and foot radiographs (36% and 39%, respectively), showed abnormalities without distinct clinical symptoms, while in the knee, ankle and elbow this proportion was lower (23%, 10%, and 6%, respectively).

The correlation between clinical symptoms and radiologic findings was analyzed further. When the overall articular severity score of the radiographed joint was related to the presence of radiologic abnormalities of these joints, the results showed a significant increase in the probability of radiologic signs with each increase in the overall articular severity score, using the logistic regression model. Because the overall articular severity score includes a score for swelling, we excluded the radiologic sign of swelling for this analysis. The odds ratio (OR) for the overall severity score was 1.4 ($P < 0.0001$). The relationship between the overall severity score and the probability of radiologic signs is given in Figure 2. A total of 155 radiographed joints had an overall severity score of 0 (no clinical signs of disease), but 20% of these showed radiologic abnormalities (marginal probability of 0.20) (Figure 2).

In explanatory univariate analysis, ORs for the presence of radiologic abnormalities were significantly increased in relation to the overall articular severity score, onset of arthritis beyond 10 years of age, IgM-RF positivity, or IgA-RF positivity (Table 5). Multivariate analysis showed a significant increase of the OR for the presence of radiologic abnormalities (excluding swelling) and IgM-RF positivity (OR 4.6, 95% confidence interval [95%CI] 1.44-14.5, $P = 0.005$) as well as HLA-B27 positivity (OR 3.0, 95% CI 1.32-6.84, $P = 0.004$). Inclusion of

Joint groups with clinical signs of disease (but no clinical arthritis) (n=130)		Joint groups without clinical signs of disease (n=155)	
No. radiographs	% abnormal	No. radiographs	% abnormal
31	48	31	23
20	45	29	10
19	21	31	39
20	45	11	36
7	0	17	6
13	8	12	0
10	40	12	0
8	0	7	14
0	0	4	50
2	0	1	0
130	32	155	20

Table 4. Distribution of radiologic abnormalities over the radiographed joints (joint groups) with "clinical arthritis" in at least one of the joints of the joint group*

Joint site	Number of radiographed joint groups with clinical arthritis	Number of radiographs with abnormalities†	Swelling	Osteopenia
Knee	42	27 (9)	20	3
Ankle	35	11 (2)	9	1
Foot	20	9 (6)	-	2
Hand	55	36 (33)	20	16
Elbow	18	6 (0)	2	-
Hip	6	1 (1)	NA	1
Sacroiliac joint	2	2 (0)	NA	-

* No abnormalities were found in the radiographs of the cervical spine, shoulder and mandible (10 films).
NA = not applicable.
† Values in parentheses are the number of joints/ joint groups with >1 radiologic sign.

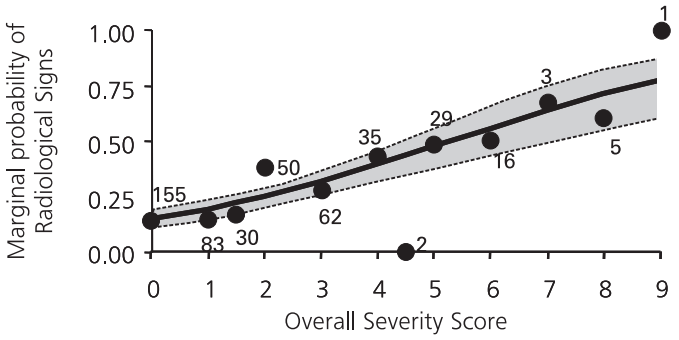

Figure 2. Correlation between clinical symptoms and presence of radiologic signs. The overall severity score of a joint is defined as the sum of the severity ratings of swelling (range 0-3), pain/tenderness (range 0-3) and limitation of motion (range 0-4) (21). In the calculation of the marginal probability of radiologic signs, the radiologic sign "soft tissue swelling" was not included. The thick solid line represents the computed marginal probability of radiologic signs given the overall severity score according to the logistic model. The dotted lines with shaded areas represent the 95% confidence intervals. Solid circles denote the observed proportion of patients with radiologic signs, and the adjacent values are the number of radiographed joints/joint groups from which the proportions are calculated.

radiologically described swelling in the score did not significantly change the results of this multivariate analysis (data not shown).

Reproducibility. To evaluate reproducibility of the readings, we reviewed 240 radiographed joints (120 at baseline and 120 at the 24-week follow-up) of 15 patients. The overall agreement on the presence of any abnormality showed a Cohen's kappa coefficient with a mean of 0.74. Kappa values of the individual features scored ranged between 0.40-0.86, as is shown in Table 6. Scores of osteopenia, growth abnormalities and swelling were the most often discrepant. On review, evaluation of osteopenia and swelling appeared highly dependent on

Specification of radiologic abnormalities, joint counts

Joint space narrowing	Growth abnormal	Bone cysts	Erosions	Abnormal joint position
5	11	-	1	-
-	1	2	-	-
1	3	4	5	-
20	13	2	10	14
-	4	-	-	-
1	-	-	-	1
2	-	-	-	-

the quality of the radiographs. In the scoring of growth abnormalities assessing advanced bone maturation or recognition of developmental growth disturbance (e.g., bone shape) appeared especially challenging.

Feasibility. Scoring of all the radiographs was time-consuming and required specific expertise on normal bone development and variants of bone development in health and disease. The current extensive consensus scoring took 2 observers ~10-20 minutes per assessment of each patient.

DISCUSSION

This study is the first step in the development of a standardized scoring system of joint radiographs in JIA. Although, in our study, radiologic damage was related to clinical disease, the data suggest that radiographs often yield important information not available on clinical assessment, and that the scoring of radiologic abnormalities may become feasible in future trials of JIA. Erosions, joint space narrowing and malalignment were readily and reproducibly identified, but soft-tissue swelling, osteopenia and growth disturbance caused more difficulty. Total scoring time was acceptable for a trial setting. Further selection of features to score and joints to examine will depend on analysis of responsiveness, which is now in progress.

Joint space narrowing and growth disturbances are considered key radiologic manifestations of JIA. These manifestations have been extensively described in several studies and reviews (6-8,29,30), with regard to the cervical spine (31), hips (32), knees (11,33,34), carpal length (14), and distal interphalangeal joints (35). A thorough knowledge of these manifestations is necessary to recognize the abnormalities on the radiographs, as is knowledge of the normal development and growth of the different joints in children and adolescents. We were able to score joint space narrowing reliably, but assessment of growth abnormalities was

Table 5. Odds ratios (OR) for the presence of at least one radiologic abnormality (excluding radiologically described swelling or swelling and osteopenia) in relation to clinical signs in 67 patients with juvenile idiopathic arthritis (JIA) by univariate analysis.*

	Radiologic abnormalities			
	Excluding soft-tissue swelling		Excluding soft-tissue swelling and osteopenia	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Overall articular severity score	1.4 (1.2-1.6)	<0.0001	1.4 (1.2-1.5)	<0.0001
IgM-RF positive	2.4 (1.4-4.0)	0.001	2.5 (1.5-4.1)	0.001
IgA-RF positive	2.3 (1.2-4.6)	0.02	2.4 (1.2-4.7)	0.01
HLA-B27 positive	2.4 (1.4-4.2)	0.001	2.3 (1.4-4.0)	0.002
ANA-positive	0.5 (0.3-0.7)	0.001	0.5 (0.3-0.7)	0.001
ESR				
< 20 mm/hour	1.0		1.0	
> 20 mm/hour	2.1 (1.1-4.2)	0.03	2.3 (1.1-4.9)	0.02
Onset age:				
< 6 years	1.0		1.0	
6-10 years	1.6 (0.9-2.7)	NS	1.5 (0.9-2.6)	NS
> 10 years	2.8 (1.7-4.5)	0.0001	2.8 (1.7-4.7)	<0.001
Disease duration:				
< 2 years	1.0		1.0	
2-5 years	1.8 (0.9-3.8)	NS	1.5 (0.7-3.4)	NS
>5 years	0.6 (0.2-1.7)	NS	0.7 (0.2-2.0)	NS
Onset type JIA				
Oligoarticular	1.0 (0.7-1.5)	NS	1.0 (0.7-1.5)	NS
Polyarticular	1.1 (0.7-1.7)	NS	1.1 (0.7-1.8)	NS

* 95% CI = 95% confidence interval; RF = rheumatoid factor; ANA = antinuclear antibodies; ESR = erythrocyte sedimentation rate; NS = not significant (significance level $P \leq 0.05$)

Table 6. Reproducibility of the radiologic scoring method*

Scored feature	Total number of evaluable radiographs†	Absolute agreement, %	Cohen's kappa‡
No signs of disease	167	90	0.74
Soft tissue swelling	126	87	0.66
Subchondral osteopenia	123	85	0.40
Joint space narrowing	126	95	0.86
Growth abnormalities	125	86	0.61
Subchondral bone cysts	117	97	0.80
Erosions	128	94	0.79
Abnormal joint position	121	95	0.76

* Two observers scored radiographs in consensus in one session; the second reading was 4 years later.

† Total number of evaluable radiographs in which the feature was scored at least once in the two sessions.

‡ See ref. 28 for description of the kappa coefficient of Cohen.

more challenging. Analysis of the radiographs that were scored discrepantly showed that descriptions and definitions of growth disturbance need further refinement. Based on our experience, an atlas with specific definitions may have to be developed to improve scoring reproducibility of this key feature in JIA.

For the clinician, soft-tissue swelling and osteopenia on the radiograph are important early signs of joint involvement in JIA (10). However, both features are best considered signs of disease activity, rather than an indication of damage (2,7,8). Although swelling was the most frequently scored radiologic sign of disease (19% of radiographed joints), scores were only moderately reliable because the quality of the radiographs varied (kappa = 0.66). Similarly, scores of subchondral osteoporosis and general osteopenia, which were shown to be highly dependent on radiologic technique, differed appreciably between sets of films and were subtle and difficult to reproduce (kappa = 0.40). Thus, both swelling and osteopenia may be of limited use in a final scoring system. Localized dual X-ray absorptiometry may be a promising alternative for the study of osteopenia (36).

We noticed bone cysts in the joints in 10% of our studied patients, and this feature showed good reproducibility (kappa = 0.80). In our study, only 15% of the patients showed erosions on the radiographs; in all but one radiograph, the erosions were found in the hands and feet. None of the erosions showed a destruction of joint surface of >50%. It is well known that erosions in children develop later in the course of the disease compared with that observed in RA, and their development depends on the type of JIA (37). In our study population, the median duration of disease was only 2 years.

Apart from the features to score, the other main issue is which joints to assess. In our study (as in other studies), knees, ankles, hands and feet were most frequently affected (10,29,33,34). In addition, hands and feet showed very diverse radiologic features. Ideally, the abnormalities in one index joint group would be a summary of the abnormalities present in other joint groups. In adult RA, hands and forefeet are widely accepted as such an index. In JIA, some studies have used carpal length as the index, but these included only patients with polyarthritis and those with systemic JIA who had clinical involvement of the wrist (13,38). In our study, only 58% of the patients had clinical wrist involvement (data not shown), and the abnormalities found in hand radiographs did not correlate well with abnormalities found in other joint groups. The same was true for the other frequently affected joints. Pending further information, we suggest studies should radiograph (and follow up) all clinically affected joints, including, as a minimum, the hands, feet, and knees.

Although univariate analysis showed a good correlation between the overall articular (clinical) severity and the presence of radiologic abnormalities, this relationship was largely unpredictable in specific joints. Many abnormalities were found in clinically uninvolved joints, especially in the hands and feet. This may be partially explained by incomplete information about the history of clinical involvement of these joints. However, we are confident that radiographs add substantial information not obtainable by physical examination.

Some interesting relationships between laboratory features and radiologic abnormalities were seen. In univariate analysis, ANA positivity was associated with the absence of radiologic

abnormalities, but this finding was not confirmed in multivariate analysis. In contrast, IgM-RF and HLA-B27 positivity were both independently associated with the presence of radiologic abnormalities. IgM-RF-positive patients with JIA are known to have a disease course similar to that of adult RA, and HLA-B27-positive patients (boys with disease onset beyond 8 years of age and with enthesitis and arthritis) are thought to have a disease course similar to that in adults with ankylosing spondylitis. One other study has also indicated that HLA-B27 positivity in JIA patients relates to a more severe course of JIA (39).

We again note that, in this first step, we did not evaluate sensitivity to change or the relationship to future joint impairment. The long-term functional outcome in the joint is said to be related to joint space narrowing, growth disturbance, and joint deformation by erosions (37). However, it is not clear what type of abnormalities were analyzed to come to this conclusion. For a further development of our scoring method, a long-term follow-up study is in progress to solve the issues of sensitivity to change and prognostication.

In conclusion, this study shows that scoring radiographs in patients with JIA is feasible and adds information about joint involvement. However, both a thorough knowledge of radiologic manifestations of JIA and knowledge of the normal development and growth of the different joints is necessary to reliably detect abnormalities on the radiographs. The choices to be made regarding methodologic issues will depend on the purpose for which imaging is done, whether it is to classify, to prognosticate, or to measure change in the joints over time, and might be different for each purpose.

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Chapter 6

A standardized assessment method of radiographs and radiographic change in juvenile idiopathic arthritis: introduction of the "Dijkstra composite score"

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ABSTRACT

Objective. To evaluate the sensitivity to change of the newly developed radiologic assessment tool, the Dijkstra score, and to develop a numeric composite score and progressor classification scheme to apply in juvenile idiopathic arthritis (JIA) trials.

Methods. A placebo-controlled trial of sulfasalazine (SSZ) in patients with oligoarticular- and polyarticular-onset JIA yielded the data for this study. Data were obtained from 418 sets of radiographs of the clinically involved and contralateral joints (at study entry and at 6 months' follow-up) from 66 JIA patients. The Dijkstra score assesses the presence or absence of swelling, osteopenia, joint space narrowing, growth abnormalities, subchondral bone cysts, erosions and malalignment. The signs were combined in the Dijkstra composite score, to assess inflammation (DI), growth (DG) and damage (DD). Progression was defined as an increase in either the DG or the DD score. Scores were evaluated among all radiographs, a standard set of films (hand, foot, and knee) and per patient. All scores were used to explore differences between the 2 treatment groups.

Results. Over time, 58% of joints remained normal, 23% remained abnormal but stable, 14% showed an increase in signs, and 5% showed a decrease in signs. Of the 66 JIA patients, 12% had normal radiographic findings throughout follow-up, 27% showed abnormalities at some sites without change, and 61% showed change in at least 1 site. Changes in the DI, DG and DD varied considerably per type of joint and occurred most frequently in joints of the standard set. DI and DG scores changed most often in the knees, while DD scores changed primarily in the hands and feet. The disease course in 8% of joints was classified as progressive. Films of SSZ-treated patients, versus the placebo group, showed less deterioration by the DD scores ($P = 0.04$), and the disease course was more often classified as nonprogressive in the SSZ group ($P = 0.037$). When progressors were defined as those who had at least one radiograph showing progression, significantly more placebo-treated patients were considered progressors ($P = 0.046$).

Conclusion. In this trial dataset, the Dijkstra composite score and the resulting progressor classification system are comprehensive and feasible tools that are sensitive to change and discriminate between clinical situations. They should now be tested by other investigators and in other datasets.

INTRODUCTION

Juvenile idiopathic arthritis (JIA)(1) can lead to destructive lesions of joint cartilage and periarticular bone. Since the introduction of more potent treatment strategies, the evaluation of radiographic joint damage has become more prominent in the assessment of disease progression in JIA (2-4). Because one of the aims of JIA treatment is to prevent or retard joint damage, and radiographs are able to document this damage, a standardized tool for the radiological evaluation of the lesions of the joints over time is needed. Several methods have been proposed to assess radiographs in JIA (5-8), but none have been tested for sensitivity to change or discrimination between treatment groups in a trial. Recently, we introduced the Dijkstra score as a standardized method to evaluate the radiographs of patients with oligoarticular- and polyarticular-onset JIA. Data were obtained from the data set of a placebo-controlled sulfasalazine (SSZ) trial performed in The Netherlands (9). All radiographs were assessed for the presence of a comprehensive spectrum of JIA radiologic features. We found the reliability, feasibility, and measurement properties of the Dijkstra score to be adequate for its purpose.

To decide whether a measure or instrument is applicable in a particular clinical setting, the OMERACT filter can be applied (10). This tool was developed for the Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative and summarizes applicability with 3 criteria: 1) truth (Does the instrument measure what it is supposed to?), 2) discrimination (Can the instrument discriminate between situations of interest?), and 3) feasibility (Can the instrument be feasibly applied in the intended setting?). We confirmed, to some degree, the truth and feasibility of the Dijkstra score in a clinical trial setting in our previous study (9). In the current study we focus on the discrimination criterion as it applies to the Dijkstra score. More specifically, we studied whether the Dijkstra score could detect radiographic change in a 6-month period, and also whether differences in change between the treatment groups could be detected. For this purpose, we propose a composite score for inflammation, damage and growth disturbances, and a classification scheme to distinguish between progressive and non-progressive radiographic joint damage.

PATIENTS AND METHODS

Data collection and scoring of radiographs. A randomized placebo-controlled trial of SSZ in patients with oligoarticular- and polyarticular-onset JIA (mean ± SD age 9 ± 4 years), performed by the Dutch JIA Study Group (3), yielded the data for this study. All conventional film-screen radiographs of the affected joints (those that are tender, painful, swollen, and/or limited in motion, as judged by the treating physician) and the contralateral joints, obtained at study entry and 6 months' follow-up, were analyzed. After completion of the trial, the radiographs were scored in chronological order in a single session by a skeletal radiologist (Piet F. Dijkstra) and a pediatric rheumatologist (MAJvR) in consensus. The readers were blinded to the subtype of JIA and the clinical condition of the patient.

The radiographs were scored in accordance with a standardized assessment method as described previously (9); this is referred to as the Dijkstra score. In summary, a maximum of 19 joints or joint groups were evaluated on radiographs: the cervical spine (1 joint), 2 mandibles, 2 shoulders, 2 elbows, 2 hands (for each hand, the joint group includes all finger, metacarpal and wrist joints), 2 sacroiliac joints, 2 hips, 2 knees, 2 ankles and 2 feet (for each foot, the joint group includes all tarsal, metatarsal, and toe joints). In the current report we use the term joint both for a large single joint and for a group of smaller joints (e.g., the hands). The following features (collectively defined as a radiological abnormality) were scored as present or absent: soft-tissue swelling, osteopenia, joint space narrowing (JSN), enlargement or other growth disturbances, subchondral bone cysts, erosions and abnormal joint position or malalignment. One joint/joint group could have a positive score for more than one feature, but each feature was only counted once (e.g. a joint/joint group could show more than one erosion, but the erosion score remained as 1).

A set of radiographs was obtained for each joint and comprised the films obtained at study entry (baseline) and those obtained at 6 months' follow-up. A standard set of films was defined as radiographs of both hands, feet and knees of 1 patient. The differences in scores over time were compared between radiologic signs, joints, and patients.

For a further standardized numeric evaluation of the data, we defined the Dijkstra composite scores for each radiographed joint as follows: Dijkstra Inflammation score (DI) score (range 0-2) is the summation of scores for swelling (range 0-1) and osteopenia (range 0-1); the Dijkstra Damage score (DD) score (range 0-3) is the summation of scores for JSN (range 0-1), bone cysts (range 0-1), and erosions (range 0-1); and the Dijkstra Growth score (DG) score is the score for growth abnormalities (range 0-1). The DI, DD, and DG scores were calculated at baseline and at follow-up for each radiographed joint and for each patient, and the values at both time points were compared. An increase in any of the Dijkstra composite scores was deemed to indicate joint deterioration, while a decrease reflected improvement. The malalignment sign was excluded from analyses, since its prevalence on the radiographs was too low to generate useful data.

Definition of progression. Joint damage was subsequently categorized as progressive when either the DD or the DG score in a joint increased. The disease course in all other joints was considered to be nonprogressive, with subclassifications of normal (both DD and DG scores of 0, with no increase), abnormal-stable (either or both scores >0, with no change), and abnormal-improved (either or both scores >0, with a subsequent decrease in either or both scores at 6 months). Patients were defined as having a progressive disease course (progressor) when at least 1 radiographed joint showed progression as defined above.

Statistical analysis. The presence of radiologic abnormalities was summarized both at the level of the various joints and at the level of the patient.

At the level of the individual joints, a marginal regression model, as implemented in the SAS statistical program, proc GENMOD (SAS Institute, Cary, NC), was used to compare different

patient groups with respect to the Dijkstra composite scores. Wald-type chi-square statistics using robust variance estimates were calculated to account for the possible correlation between joints from the same patient. The same approach was used to test the differences between baseline and follow-up radiographs, and to assess associations between the different composite scores (reflecting radiologic changes) per joint. The logistic regression approach in proc GENMOD was used to compare the percentage of progressive/non-progressive joints between different patient groups. At the level of the individual patients, ordinary linear and logistic regression analyses were used to evaluate the effect of treatment and other patient characteristics on the Dijkstra composite scores, and on the percentage of progressive/non-progressive patients. A *P* value of less than or equal to 0.05 was considered significant.

RESULTS

Data set. The original placebo-controlled SSZ trial included 69 patients with JIA. For the present study 3 patients were excluded (1 because of reclassification as having systemic JIA, and 2 because of missing radiographs). Therefore, the data comprised 418 sets of radiographs from 66 patients. At study entry, all affected and contralateral joints were radiographed; of the baseline films, 288 (69%) originated from joints with clinical symptoms (swelling, pain, limitation of motion). The patients' characteristics are listed in Table 1. At baseline, 10 patients (15%) had no abnormalities on their radiographs. The mean number of sets of radiographs (a single joint radiographed at baseline and at follow-up) per patient was 6.3 (SD 3.7, range 2-15). The sets of radiographs consisted of radiographs of the knees (23%), hands (20%), ankles (18%), feet (15%), and other joints (24%).

Radiographic findings. *Changes overall.* The proportion of radiographs showing abnormalities was stable over time: 35% of radiographs showed swelling and osteopenia at baseline versus 38% at follow-up, and 24% did not show these signs at baseline versus 26% at follow-up. After 6 months, 58% of the radiographed joints remained normal, 23% remained abnormal but stable, 14% showed an increase in signs, and 5% showed a decrease in signs; if the presence of swelling and osteopenia are excluded from the score, these proportions change to 71% remaining normal, 18% abnormal but stable, 3% showing an increase in signs, and 8% showing a decrease in signs.

Changes per joint. The knees, hands and feet were most likely to change, especially from normal to abnormal in the latter 2 sites (Table 2). The knees were most likely to change from abnormal back to normal. With regard to the separate radiological signs scored according to the Dijkstra score in the different types of joints (Table 3), all signs showed changes over time in the hands and knees. In the joints of the feet, all radiologic signs showed changes except for swelling. Swelling and growth abnormalities changed most often in the knees.

Changes per patient. Of the 66 patients with JIA, 8 (12%) had normal radiographic findings throughout follow-up, 18 (27%) showed abnormalities at some sites without change, and 40

Table 1. Characteristics at study entry of 66 patients with juvenile idiopathic arthritis who participated in the placebo-controlled trial of sulfasalazine*

Characteristic	Value
Age, mean ± SD (range) years	9.0 ± 4.1 (2.5-17.6)
Female	45 (68)
Disease onset before age 6 years	35 (53)
Disease onset between 6 and 10 years	16 (24)
Disease onset beyond age 10 years	15 (23)
Disease duration, months	
Median (IQR)	24 (10-40)
Range	5-176
Polyarticular-onset type JCA†	29 (44)
Oligoarticular-onset type JCA	37 (56)
>4 joints with clinical arthritis at study entry‡	41 (62)
Antinuclear antibodies present	33 (50)
IgM rheumatoid factor present	9 (14)
HLA-B27 positive	11 (17)
Intraarticular corticosteroid use ever	29 (44)
Disease-modifying antirheumatic drug use ever	5 (8)
Systemic corticosteroids use ever	2 (3)

* Except where otherwise indicated, values are the no. (%) of patients.
IQR= interquartile range
† The criteria of the European League Against Rheumatism for juvenile chronic arthritis (JCA) were used at the original study inclusion (3)
‡ Clinical arthritis is defined as the presence of swelling or limitation of motion, plus pain upon movement or tenderness. The total number of patients includes 12 patients with oligoarticular-onset JCA and a polyarticular disease course, and 1 patient with polyarticular-onset JCA with <5 joints with clinical arthritis at study entry.

Table 2. Changes from baseline to follow-up in overall status per joint according to the Dijkstra score*

		Dijkstra score including swelling and osteopenia (n = 418)			
		Normal at baseline (n = 270)		Abnormal at baseline (n = 148)	
Joint site	No. of sets	Normal at follow-up	Abnormal at follow-up	Abnormal at follow-up	Normal at follow-up
Knee	95	43	7	40	10
Hand	83	38	7	53	2
Foot	62	56	5	36	3
Ankle	76	67	7	25	1
Elbow	38	68	18	11	3
Shoulder	24	96	0	0	4
Hip	22	86	0	14	0
Cervical spine	14	100	0	0	0
Sacroiliac joint	4	50	0	50	0

*Values are the percentage of radiograph sets. Changes are defined as going from normal to abnormal or vice versa. The Dijkstra score includes scores for the presence of swelling, osteopenia, joint space narrowing, growth abnormalities, bone cysts, erosions, and abnormal joint position. One joint could have more than 1 abnormality.

(61%) showed change in at least 1 site. Of these 40 patients whose radiographs showed change, only 2 had normal findings at baseline and developed abnormalities at follow-up, while the other patients already had abnormalities on the radiographs at baseline. Changes in the number of scored signs occurred in 24 patients, of whom 13 showed an increase and 11 showed a decrease in signs. If the presence of swelling and osteopenia are excluded from the score, the number of scored signs changes to 11 patients with an increase and 3 with a decrease in signs.

Progression of joint damage. Changes in the clinical joint scores (swelling, pain, limitation of motion, overall clinical severity score) showed no correlation with changes in the radiologic joint scores (results not shown). The changes in Dijkstra composite scores DI, DD en DG varied considerably per type of joint and occurred most frequently in the knees, hands and feet (Table 4). The DI and DG scores (inflammation and growth abnormalities) changed most often in the knees, while the DD scores (joint damage) changed most often in the hands and feet. Patients with different prognostic profiles (HLA-B27 positive or IgM rheumatoid factor positive (9)) and patients with availability of films from the standard set (hands, feet, and knees) showed comparable degrees of changes in the Dijkstra composite scores (results not shown).

With regard to changes over time and disregarding treatment group, only the changes in the DD score were statistically significant ($P = 0.035$). Since most changes occurred in the standard set, there was little correlation between these and the (few) changes in the other joints, especially when considered according to the DI and DG scores. We did see some changes in the DD score outside the standard set, but in all instances this was accompanied by DD changes within the standard set. The disease course in 8% of joints was classified as progressive because either the DG or the DD score increased (Table 5). Among the nonprogressors, roughly 74% were subclassified as normal, 15% as abnormal-stable, and 3%

Dijkstra score excluding swelling and osteopenia (n = 418)			
Normal at baseline (n = 319)		Abnormal at baseline (n = 99)	
Normal at follow-up	Abnormal at follow-up	Abnormal at follow-up	Normal at follow-up
73	5	14	8
45	6	48	1
56	7	34	3
92	3	0	5
78	11	11	0
96	0	0	4
86	0	14	0
100	0	0	0
50	0	50	0

A set of radiographs includes a joint radiographed at baseline and at 6 months' follow-up. All radiographs of joints having at least 1 radiologic abnormality according to the Dijkstra score are classified as abnormal.

Table 3. Changes from baseline to follow-up in scored radiologic signs according to the Dijkstra score*

Joint site†	No. of available film sets	Radiologic sign					
		Swelling	Osteopenia	Joint space narrowing	Growth disturbances	Bone cysts	Erosions
Knee	95	18	3	3	13	1	1
Hand	83	7	6	6	6	11	7
Foot	62	NC	7	3	2	3	15
Ankle	76	9	NC	NC	NC	3	NC
Elbow	38	5	5	NC	3	5	3
Shoulder	24	NC	NC	NC	NC	NC	4
All	378	8	4	3	5	4	5

* Values are the percentage of radiograph sets showing changes. NC = no change.
† No changes occurred in the presence of separate radiologic signs over time in the radiographs of the cervical spine (14 sets), hips (22 sets) and sacroiliac joints (4 sets).
Changes in the presence of malalignment occurred in 3 sets of hand radiographs (not shown).

as abnormal-improved. In the standard set, the proportion considered normal was somewhat lower at 62%, whereas it was higher (90%) in the remaining films. These results suggest that restriction of assessment to the standard set does not lead to important loss of information, and may even enhance the signal-to-noise ratio.

Comparison of treatment groups. Finally, we explored the data to identify a possible treatment effect of SSZ on the outcome displayed by the radiographs. In this study, 187 (45%) of the sets of radiographs originated from 31 placebo-treated patients and 231 (55%) were from 35 SSZ-treated patients. Significantly less deterioration, as evidenced by changes in the DD scores, occurred in the SSZ-treated patients compared with the placebo-treated patients ($P = 0.04$), whereas the differences in the DI and DG scores were not significantly different between treatment groups. In the standard set (65 patients, 240 hand/foot/knee radiographs), the SSZ group consistently showed less deterioration than the placebo group, according to the DI, DG and DD scores, but the difference was only marginally significant for the DD score ($P = 0.052$).

Classification of the radiologic change as progressive or nonprogressive improved the power of the comparison. When we classified films of the joints as progressive or non-progressive, we found that 12% of the joints of the placebo group could be classified as progressive compared with 4% of the joints of the SSZ group ($P = 0.037$); the corresponding values from the films of the standard set were 16% and 7%, respectively ($P = 0.025$) (Table 6). We also analyzed the radiologic change at the individual patient level. When patients with at least 1 radiograph showing progression were classified as progressors, significantly more placebo-treated patients were considered to be progressors ($P = 0.046$). This difference between the treatment groups was no longer significant when the analysis was restricted to hand/foot/knee radiographs from patients with availability of radiographs from the standard set ($P = 0.15$).

Table 4. Changes from baseline to follow-up in the Dijkstra composite score of the radiographed joints*

Dijkstra score, change over time	All joints (n = 418)	Knee (n = 95)	Hand (n = 83)	Foot (n = 62)	Ankle (n = 76)	Elbow (n = 38)	Shoulder (n = 24)
Inflammation							
DI unchanged	89	79	88	94	91	89	100
Normal	73	54	58	92	67	89	100
Abnormal	16	25	30	2	24	-	-
DI increased	6	8	7	3	8	9	-
Normal to abnormal	4	6	3	3	7	9	-
Increase in abnormality	2	2	4	-	1	-	
DI decreased	5	13	5	3	1	2	-
Abnormal to normal	5	13	5	3	1	2	-
Decrease in abnormality	-	-	-	-	-	-	-
Damage							
DD unchanged	92	95	86	85	97	92	96
Normal	83	87	70	65	93	92	96
Abnormal	9	8	16	20	4	-	-
DD increased	6	5	12	10	3	8	-
Normal to abnormal	4	4	4	8	3	8	-
Increase in abnormality	2	1	8	2	-	-	-
DD decreased	2	-	2	5	-	-	4
Abnormal to normal	1	-	2	3	-	-	4
Decrease in abnormality	1	-	-	2	-	-	-
Growth							
DG unchanged	96	87	94	98	100	98	100
Normal	86	80	72	85	99	87	100
Abnormal	10	7	22	13	1	11	-
DG increased	2	3	6	2	-	2	-
Normal to abnormal	2	3	6	2	-	2	-
DG decreased	2	10	-	-	-	-	-
Abnormal to normal	2	10	-	-	-	-	-

*Values are the percentage of radiograph sets. The Dijkstra composite scores were defined as follows: DI = Dijkstra inflammation composite score (range 0-2), includes scores for swelling (0-1) and osteopenia (0-1); DD = Dijkstra damage composite score (range 0-3), includes scores for joint space narrowing (0-1), bone cysts (0-1) and erosions (0-1); DG = Dijkstra growth abnormalities score (range 0-1), includes the score for presence of growth abnormalities (0-1). The change in Dijkstra composite scores over time was calculated as follows: [value of Dijkstra score at follow-up] - [value of Dijkstra score at study initiation].
No changes occurred in the composite scores of the radiographs of the cervical spine (14 sets), hips (22 sets) and sacroiliac joints (4 sets).

Table 5. Classification of radiologic change from baseline to follow-up into progressive and non-progressive change*

Classification of radiologic change, definition	All radiographed joints (n = 418)	Only radiographs of the standard set (hand/foot/knee) (n = 240)	All other radiographed joints (n = 178)
Progressive			
-Increase in DD or DG score	8	11	3
Nonprogressive			
-Normal (DD and DG score 0, no increase)	74	62	90
-Abnormal - stable (DD or DG score >0, no change)	15	22	6
-Abnormal - improved (DD or DG score >0, decrease in DD or DG score at 6 months)	3	5	1

* Values are the percentage of radiographs. The outcome distribution of progressive versus non-progressive radiologic change differed significantly (P = 0.02) between radiographs of the standard set (hand/foot/knee) and all other joints. See Table 4 for definitions.

Table 6. Classification of outcome on the radiographs from patients treated with sulfasalazine (SSZ) versus placebo in the clinical trial*

Classification of radiologic change, outcome subclassification	All radiographed joints (n = 418)		Only radiographs of the standard set (hand/foot/knee) (n = 240)	
	Placebo treatment radiographs (n = 187)	SSZ treatment radiographs (n = 231)	Placebo treatment radiographs (n = 104)	SSZ treatment radiographs (n = 136)
Progressive	23 (12)	9 (4)	17 (16)	9 (7)
Nonprogressive				
-Normal	135	173	66	82
-Abnormal - stable	25	39	18	35
-Abnormal - improved	4	10	3	10

* Values are the no. (%) of radiographs. The 187 (45%) of the sets of radiographs originated from 31 placebo-treated patients, and the 231 (55%) from 35 SSZ-treated patients (P = 0.54). See Table 5 for definitions of outcome. The outcome distribution of progressive versus nonprogressive (normal, abnormal-stable or abnormal-improved taken together) classifications of radiologic change differed significantly (P = 0.037) between radiographs of placebo- and SSZ-treated patients, and P = 0.025 between treatment groups for radiographs of the standard set.

DISCUSSION

This study demonstrates that the Dijkstra scoring method of assessing radiographs in oligoarticular- and polyarticular-onset JIA can detect change over a trial period of 6 months. Changes could be demonstrated at the level of 1) the presence of radiologically scored signs, 2) the number of scored signs per joint, and 3) the number of scored radiologic signs per patient. In addition, the differences between placebo and SSZ treatment groups, many of

which were statistically significant, could be demonstrated at these 3 levels. Finally, a simple classification scheme to identify progressors and nonprogressors proved discriminative between the treatment groups.

Reduction in the number of radiographs to a standard set of images of the hands, feet, and knees appears feasible without losing essential information. Radiologically scored abnormalities changed most often in the knees, hands and feet. We therefore propose that the radiological assessment of all joints of this standard set be carried out in clinical trials, regardless of disease activity.

Most radiographs showed additional radiologic features at follow-up, but in some radiographs, abnormalities present at baseline were not present at follow-up. This feature of normalization occurred in several types of joints, but most often in the knees. We assume that an increase in number of scored signs reflects disease progression, but a stable number or a decrease in the number of scored signs does not inevitably reflect disease improvement (e.g. JSN or erosions can replace growth abnormality). Only joints without remaining signs have unquestionably improved. In addition, one should be aware that in the Dijkstra scoring system, an increase in identical signs within joints (e.g. increase in number or size of erosions) is not reflected in an increase in the number of scored signs (score for erosions remains 'present' = '1').

Changes were evident in all aspects of the score, comprising inflammation (swelling and osteopenia), pathologic changes in the cartilage (JSN and growth abnormalities) and those in the bone (growth abnormalities, bone cysts and erosions). In our previous study, we demonstrated that scores for swelling and osteopenia were only moderately reliable (9). Despite detectable change, we still believe that both swelling and osteopenia are of limited value in a scoring system. Nevertheless, at this stage of scoring development, we consider it too early to reject these radiologic findings for further evaluation.

Changes in growth abnormalities were detected in several types of joints; in particular, in the hand and knee, growth abnormalities both regressed and appeared during the follow-up period. This sign is considered a key manifestation of JIA (8,11,12), but in our hands its reproducibility was moderate (9). Definitions of growth disturbance therefore need further refinement (e.g., an atlas of reference films) to improve the value in a scoring system.

JSN is also considered a key manifestation in JIA. JSN showed a reliable reproducibility in our previous study and in other studies (9,13). In the present study, changes in JSN were demonstrated in all joints of the standard set. Scores for bone cysts and erosions changed in several joints and appeared reliably reproducible in our previous study (9). Quantification and refinement of the erosion and JSN scores might further improve the performance of radiologic scoring in JIA, consistent with that achieved in rheumatoid arthritis RA (14). Future studies with a longer period of follow-up are needed to elaborate on this subject. Changes in malalignment were only rarely detected in the hands, and we therefore have too little data to evaluate the value of scoring this sign in JIA.

To be applicable in trials, we developed a numeric score, the Dijkstra composite score, comprising separate values for inflammation, growth abnormalities and damage. In our

opinion, these 3 scores represent distinct radiologic information. The results of our study show that DI, DG, and DD scores changed significantly over time and elucidated specific changes in radiographs at the level of the joints and at the level of the patient. The study also demonstrates that the Dijkstra composite score adequately reflects the radiologic change in different patient groups.

For a further evaluation of change, we categorized the radiologic change into progressive or nonprogressive. In evaluations of radiologic outcome in adult RA trials, the progressor classification may provide a useful summary of the data per patient, although its significance for long-term prognosis remains to be determined (15-17). We posited that in JIA, clinically meaningful radiologic change would imply progression of either growth abnormalities or damage. Therefore, we defined progressive radiologic change as an increase in either the DG or the DD score in a joint. In our study, application of this proposed definition for classification resulted in a distinct discrimination of radiographs originating from placebo-treated and SSZ- treated patient groups. Moreover, individual patient-based analysis showed a significant difference between progressor and nonprogressor patients to the advantage of SSZ-treated patients. These findings must be interpreted with caution, since the trial was not designed to evaluate differences in damage progression. Nevertheless, the radiologic findings are consistent with the clinical findings in the trial (3), and with the effects of SSZ in adult RA (18,19). Thus, the findings appear to confer some additional construct validity to the composite scores and subsequent classifications.

In summary, this study completes the initial validation phase of the Dijkstra score. We suggest that it is the first radiologic measure in JIA to pass the OMERACT filter of truth, discrimination and feasibility, at least in the setting of a placebo-controlled trial in oligoarticular- and polyarticular-onset JIA. Future studies by other investigators and in other data sets should put this measure to the test. For this purpose, we intend to produce training materials, and we will further validate the scoring method on the basis of a long-term follow-up of patients in the trial.

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Chapter 7

Long-term outcome of juvenile idiopathic arthritis following a placebo controlled trial: sustained benefits of early sulfasalazine treatment

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Submitted

ABSTRACT

Objective. A previous 24-week randomized trial demonstrated that sulfasalazine (SSZ) treatment was superior to placebo (PLAC) in suppressing disease activity in patients with oligoarticular- and polyarticular-onset juvenile idiopathic arthritis (JIA). The current study determines the long-term outcome of the trial participants and evaluates whether the benefits of SSZ allocation are sustained over time.

Methods. Between 2001 and 2003, 32 SSZ and 29 PLAC patients (90% of all patients) were examined clinically and by chart review, median 9 years (range 7-10) after trial inclusion. In the follow-up assessment variables of the American College of Rheumatology Pediatric 30 (ACR Pedi 30) criteria were collected.

Results. After the trial patients had been routinely followed in rheumatology referral centers, and treated at the discretion of the attending physician. Almost all patients continued or started DMARDs (SSZ 91%, PLAC 93%; SSZ treatment in about 80%). DMARD treatment was less intensive in the SSZ group as evidenced by a significantly shorter duration of SSZ use (median 2.5 vs. 5.2 years; $P = 0.02$), and a trend towards lower percentage of methotrexate users, median duration of methotrexate use, number of used DMARDs, duration of use of different other DMARDs, and percentage of patients on current DMARD treatment. Prednisone was rarely used. More than one-third of patients reported long periods of noncompliance with DMARD treatment in both groups.

At follow up most patients (74%) had active joints and 30% showed active polyarthritis. Despite lower treatment intensity, almost all outcome scores were much better for SSZ than for PLAC patients. Differences were significant for the number of active joints, patients' overall well-being, number of patients experiencing clinical remission off medication, patients in remission or ACR Pedi 30 responder at follow-up and duration of remission episodes. In additional explanatory analyses, DMARD treatment compliance positively correlated with an ACR Pedi 30 response (odds ratio (OR) 3.8, 95% confidence interval (CI) 1.1-13.4); $P = 0.03$). Adjusted for compliance, a SSZ patient was 4.2 times as likely as a PLAC patient to be an ACR Pedi 30 responder at follow-up (95% CI 1.3-14.3; $P = 0.02$).

Conclusion. This study shows that effective suppression of disease activity by SSZ treatment early in active disease in JIA patients has beneficial effects that persist for many years. Given these results, compliance with DMARD treatment deserves serious attention.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic inflammatory arthritis that begins before the age of 16 years and is quite distinct from adult rheumatoid arthritis (RA). The clinical disease course varies widely depending on the subtype of JIA and is difficult to predict (1-6). Some patients experience disease remission before adult age, while others develop progressive joint destruction and serious functional disability (7-10). In an effort to reduce long-term morbidity, the attitude toward institution of DMARD treatment in JIA changed in the early nineties (11). Since then, antirheumatic drug treatment in JIA has moved to institution of more aggressive therapy early in the disease course in line with treatment in RA. The short-term results of this strategy seem favorable, but the long-term effects are unknown (12).

In the period 1992-1994 we conducted a 24-week randomized placebo-controlled sulfasalazine (SSZ) study to test its efficacy and safety in oligoarticular- and polyarticular-onset JIA patients (13). This trial showed SSZ to be superior to placebo in suppressing disease activity. After the trial, participants were treated without further protocol in Dutch pediatric rheumatology referral centers and had optimal opportunities for receiving contemporary care. We therefore consider this Dutch cohort as a representative group of JIA patients who had a relatively early opportunity of DMARD treatment in an active phase of their disease in the nineties. The aim of this study was to describe the outcome of this well-defined study cohort of JIA patients and to determine whether early intervention with SSZ would lead to long-term benefits in disease activity and function.

PATIENTS AND METHODS

Design. The study is a cohort follow-up of a randomized trial. Patients and their clinical charts were examined once by the principal investigator in a series of site visits in rheumatology referral centers between 2001 and 2003.

Patients. All patients participating in the multicenter, double-blind, randomized, placebo-controlled SSZ trial (SSZ-trial) of 24 weeks' duration performed by the Dutch Juvenile Idiopathic Arthritis Study group in the period 1992 - 1994, were invited to take part in the follow-up study. To be eligible for enrolment in the original SSZ-trial, patients had to meet the European League Against Rheumatism (EULAR)(14) criteria for oligoarticular- or polyarticular-onset JCA, further referred to as oligoarticular- and polyarticular-onset JIA according to the current nomenclature (15,16). The age limits were 2 - 18 years, with onset of JIA before the age of 16. Further inclusion criteria were at least 1 joint with active arthritis (defined as a joint with swelling or a joint with pain and limitation in range of motion [LOM])(17), and an insufficient response to nonsteroidal anti-inflammatory (NSAID) drug therapy. Concurrent treatment with prednisone and prior treatment with SSZ were not allowed. Further details of the SSZ-trial have been reported previously (13).

For the follow-up study, informed consent was sought from the patients and parents according to the legal requirements. Eligible patients who were not participating in the follow-up study were asked permission to retrieve the most recent data on disease activity and medication use from their medical records.

Procedures. The database of the SSZ-placebo controlled trial was used for data on onset of arthritis; randomization to PLAC or SSZ treatment; and joint scores, general assessments, laboratory data and adverse events during the trial. Patients' medical charts were retrospectively reviewed for the following information: clinical data (presence of arthritis; occurrence of uveitis; concomitant diseases and medical problems which came to the attention of the treating physician); laboratory data (presence of rheumatoid factor); treatment data (NSAIDs, DMARDs, systemic corticosteroids, immunosuppressive drugs, anti-tumor necrosis factor treatment (anti-TNF); reason for change of treatment drug; reported compliance with DMARD treatment; intra-articular corticosteroid treatment and joint surgery. A patient was scored as non-compliant with DMARD treatment when the physician on at least 2 occasions, more than 6 months apart, had recorded that the patient did not take DMARDs as prescribed in the past evaluation period because of resentment (either by the patient or parents) against its use. Generally, between the ages of 16 and 19 years, patients were transferred to adult rheumatology departments located in the same hospitals as the pediatric centers, or to adult rheumatologists related to the Dutch Juvenile Idiopathic Arthritis working group. Medical records and/or correspondence were thus available for all patients with active disease beyond their follow-up period in the pediatric clinics.

Outcome assessments. Participants were asked to visit one of the centers for physical examination, completion of questionnaires, and laboratory assessment. Investigator (MVR) performed the physical examinations, and questionnaires were completed with the assistance of a research nurse (EDW-T). During the follow-up assessment, the principle investigator was blinded to the treatment assignment of the participant in the SSZ-trial. The physical examination included measurement of body height and weight, a joint assessment (either swollen, tender/painful, or limitation in range of motion [LOM])(17) and a physician's global assessment of disease activity on a 100 mm visual analogue scale (MD global VAS) (anchoring words 0 = inactive, 100 = very severe) in conjunction with a graded score (PGAS)(0 = none; 1+ = very low; 2+ = low; 3+ = moderate; 4+ = active; 5+ = very active) for comparison with SSZ-trial data. All measures related to the assessment of the joints were reported as a joint count (18,19).

Functional ability. To test functional ability, all participants below the age of 18 years were asked to complete the Dutch version of the Childhood Health Assessment Questionnaire (CHAQ)(20), and participants above the age of 18 years to complete the Dutch version of the Health Assessment Questionnaire (HAQ)(21). These two questionnaires were chosen because they use age appropriate activities ranging from childhood to adulthood and can be analyzed together (8,22,23). The CHAQ and HAQ scores (C-HAQ scores) were summarized in

the disability index that ranged from 0 – 3 with higher scores meaning higher disability (23). For facilitation of comparison with other outcome studies, the C-HAQ scores were divided into 4 categories of disability: 0 = none; 0 to 0.5 as mild; 0.6 to 1.5 as moderate, and > 1.5 as severe (8). Discomfort was assessed by the completion of a 100-mm VAS for the evaluation of pain (anchoring words 0 = no pain; 100 = very severe pain) and a 100-mm VAS (anchoring words 0 = very well; 100 = very poor) for the evaluation of overall well-being.

Laboratory evaluation. HLA-B27 data and immunoglobulin M rheumatoid factor (IgM-RF) concentrations during the disease course were retrieved from medical records. Follow-up study samples were locally measured for erythrocyte sedimentation rate (ESR) and, together with stored samples from the SSZ-trial, centrally measured for C-reactive protein (CRP) and IgM-RF. CRP was measured using a high sensitive latex-enhanced assay supplied by Roche Diagnostics (Almere, The Netherlands) on a Hitachi 911 analyzer (Roche Diagnostics), according to the manufacturer's instructions. IgM-RF was measured using an in-house enzyme linked immunosorbent assay and an ES 300 analyzer (Roche Diagnostics; Mannheim Germany).

Definitions. The preliminary criteria for inactive disease and clinical remission of JIA were used to evaluate outcome (24). We recorded clinical remission on medication (inactive disease for a minimum of 6 months)(24) solely at the follow-up visit, whereas clinical remission off medication (inactive disease for a minimum of 12 months off medication)(24) was registered both at the follow-up visit and for the time interval between the start of the SSZ-trial and review for follow-up.

To evaluate the overall outcome in comparison with SSZ trial inclusion, an adaptation of the ACR Pediatric 30 definition of improvement (ACR Pedi 30) (25) was made. Not all original trial data were comparable with follow-up data; in the trial, parents recorded patients' general assessments, and data on functional ability were not collected. We included the following variables of the ACR Pedi 30 in the overall evaluation: (1) number of active joints, (2) number of limited joints, (3) physician's global assessment of disease activity (PGAS), and (4) erythrocyte sedimentation rate (ESR). Patients were classified as improved when they showed at least 30% improvement in 3 of 4 afore mentioned variables, and not one of the variables could be worsened by more than 30%.

Statistical analysis. Data were collected on prepared forms and entered into a database program (Access); analyses were performed using SPSS. Analyses were based on data collected during the SSZ-trial (13) and follow-up study. In the SSZ-trial data were analyzed according to the intention-to-treat principle and missing measurements were imputed by carrying the last observation forward. Patients without baseline measurement on a certain item were excluded for the analysis of that specific item. Measures with a normal distribution were expressed as means and SD, otherwise medians and ranges were presented. For comparisons of means, the Student's T-test was used; medians were compared by non-parametric tests. Non-parametric

tests were used to evaluate changes of the individual patients and joint scores over time: Friedman/Cochran's Q test for multiple comparisons and Wilcoxon Signed Rank/Mc Nemar test for paired related samples. Overall differences in outcome between the JIA subgroups were tested using non-parametric analysis: the Fisher´s exact, Mann Whitney, Kruskal-Wallis or Chi-square test where appropriate.

At follow-up, individual outcome was described using the physicians' disease activity score (dichotomized with group median PGAS level as cut off value) and ACR Pedi 30 improvement status. Logistic regression analysis with forward selection was used to evaluate the association of outcome with patient characteristics and treatment related variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Variables tested univariately (Chi square and T-test where appropriate) were: oligoarticular- or polyarticular-onset type of JIA, sex, age at onset, JIA RF positive subtype classification, JIA duration before introduction of DMARD therapy, number of used DMARDs in the follow-up period, duration of SSZ treatment, duration of MTX treatment, reported DMARD therapy compliance, JIA duration at follow-up, and randomization to SSZ or PLAC in the trial; followed by a multivariate model to determine the independent factors related with outcome. For all analyses, a *P* value of less than or equal to 0.05 was considered as significant.

RESULTS

Cohort. In the original SSZ-trial, 69 oligoarticular- and polyarticular-onset JIA patients were enrolled (13). One patient was evaluated as ineligible and excluded from trial analysis. For the follow-up study, 68 patients were eligible, and of these, 67 could be contacted. Five eligible JIA patients refused a follow-up assessment but allowed retrieval of actual clinical data from their medical charts. Another one patient had a change in diagnosis; her symptoms were classified as Wegener's vasculitis 7 years after enrolment in the SSZ-trial. Regarding the whole cohort of 66 (99%) eligible contacted JIA patients the outcome was as follows: 10 patients (15%) in clinical remission off medication, 7 patients (11%) in clinical remission on medication and 49 patients (74%) with active disease. DMARDs (including systemic corticosteroids, immunosuppressive treatment and anti-TNF) were currently in use by 42 of 66 patients (64%). NSAIDs were taken on a regular basis by 36 of 66 patients (55%).

Treatment groups. In the original trial, 34 patients were randomized to PLAC and 35 to SSZ treatment. In the present follow-up study, 29 (85%) of the PLAC and 32 (91%) of the SSZ patients participated ($P = 0.48$). The five patients that refused further follow-up examinations included: one male (PLAC group, 22 years) with clinical remission off medication since 5 years, and 4 girls (3 PLAC and 1 SSZ group, mean age 14 years, range 11-16) with current active disease and actual DMARD treatment. Thus, 61 patients (90%) underwent a complete follow-up assessment. In this group outcome was comparable with that of the whole cohort (Fisher's exact test): 9 patients (15%) in clinical remission off medication; 7 patients (11%) in

Table 1. Characteristics of juvenile idiopathic arthritis trial cohort after median 9 years follow-up, by original treatment group*

Variable	Placebo group n = 29	SSZ group n = 32	*P*-value
Females	20 (69%)	21 (66%)	0.8
Age, median yrs (range)	19 (10-23)	16 (10-25)	0.1
Disease duration, median yrs (range)	10 (8-20)	11 (8-23)	0.3
Onset type JCA (EULAR classification)(14)			
- oligoarticular	15 (52%)	18 (56%)	0.8
- polyarticular	14 (48%)	14 (44%)	
Antinuclear antibody positive at onset	12 (46%)	16 (52%)	0.8
Age at onset JIA, median yrs (range)	8 (2-14)	3 (1-15)	0.02 §
Age at start SSZ trial inclusion, median, yrs (range)	11 (3-15)	8 (3-17)	0.1
Disease duration at start DMARD therapy: median, yrs (range)†	1.8 (0.5-12)	2.1 (0.4-13.2)	0.6
- oligoarticular-onset JCA patients	2.5 (0.5-12.3) ‡	3.0 (0.5-13.2) ‡	0.8
- polyarticular-onset JCA patients	1.1 (0.7-5.5)	1.5 (0.4-6.2)	0.6
Diagnosis of uveitis during disease course	3 (10%)	9 (28%)	0.08
Current JIA subtype classification (ILAR classification)(17)			
- oligoarticular persistent	4 (14%)	4 (13%)	0.8
- oligoarticular extended	7 (24%)	9 (28%)	0.7
- polyarticular rheumatoid factor negative	8 (28%)	8 (25%)	0.8
- polyarticular rheumatoid factor positive	7 (24%)	3 (9%)	0.1
- arthritis and psoriasis	-	2 (6%)	0.2
- arthritis and enthesitis	2 (7%)	5 (16%)	0.3
- other arthritis	1 (3%)	1 (3%)	0.9

* Values are the number (percentage) of patients unless otherwise indicated. SSZ = Sulfasalazine
† At follow-up, 2 Placebo allocated patients had never used DMARDs
‡ In both treatment groups, disease duration before initiation of DMARD therapy was significantly longer in oligoarticular- compared to polyarticular-onset JCA patients ($P = 0.002$)
§ SSZ allocated patients were significantly younger at disease onset but were of similar age at SSZ trial inclusion. When all rheumatoid factor positive JIA patients were excluded from analysis (n = 10), all characteristics were roughly similar in both treatment groups (data not shown)

clinical remission on medication; 45 patients (74%) with active disease; 38 patients (62%) on DMARD therapy, and 33 patients (54%) with regular use of NSAIDs.

Patient characteristics. The 61 participants in the follow-up study were examined at a median age of 18 years (range 10-25) and median disease duration of 10.7 years (range 8-23). The median interval between SSZ-trial inclusion and the follow-up visit was 9 years (inter quartile range (IQR) 8-9 years). Patient characteristics are listed in Table 1 and were comparable between PLAC and SSZ allocated patients except for a lower age at JIA onset ($P = 0.02$) of the SSZ group. When rheumatoid factor positive patients (n = 10) were excluded from analysis, all patient characteristics were roughly similar (n = 51; data not shown). In both treatment groups, DMARDs were introduced significantly later in oligoarticular- compared to polyarticular-onset JIA patients ($P = 0.002$).

Changes in classification of JIA subtype between trial inclusion and follow-up assessment occurred in 11 patients: 9 patients developed a polyarticular pattern of joint involvement whereas it was oligoarticular in the original trial, in 2 patients psoriasis was diagnosed during the follow-up period (including one patient with development of polyarticular joint involvement), and 1 patient changed into rheumatoid factor positive disease.

Comorbidity was present in 13 patients: diabetes mellitus type 1 (2 patients), constitutional eczema (4 patients), asthma (4 patients), down syndrome with celiac disease (1 patient), chronic fatigue syndrome (1 patient), epilepsy (1 patient), psychological disorders (2 patients), congenital double ureteric system (1 patient). Changes in JIA subtype classification and presence of comorbidity were not significantly different between treatment groups.

General physical outcome. *Growth.* At follow-up, patients had a mean body height below the normal range of the Dutch age adjusted growth standard curves with a mean body height standard deviation score (SDS) of –0.55 (range –3.36 to + 1.75; $P < 0.001$ one sample T); the bodyweight was within the normal range (26). *Menarche.* The mean age for menarche was 13 years (range 10-15) in 34 out of 41 females, which was concurrent with the mean age for menarche in the Netherlands (26). *Uveitis* had occurred in 12 (20%) patients and 2 patients underwent cataract surgery.

Table 2. Long-term outcome of 61 patients with juvenile idiopathic arthritis who participated in a randomized placebo-controlled sulfasalazine trial, median 9 years after trial participation in comparison with original trial data*

Variable	Trial baseline	End of trial (24 weeks)	Follow-up (median 9 years)	Differences between End of trial and Follow-up *P*- value
General assessments:				
Active joints (range 0-71)	5 (3-11)	2 (1-7)	2 (0-6)	n.s.
Limited joints (range 0-67)†	4 (1-7)	2 (1-5)	5 (2-12)	<0.001
Physician's score of disease activity (range 0-5)‡	3 (3-4)	2 (1-3)	2 (1-3)	n.s.
Erythrocyte sedimentation rate mm/hour	27 (11-43)	11 (6-22)	8 (5-22)	n.s.
C- reactive protein mg/l	6 (1-29)	2 (1-11)	2 (1-6)	n.s.
Number (%) of patients with:				
No active joints	0	14 (23%)	16 (26%)	n.s.
No limited joints	6 (10%)	9 (15%)	6 (10%)	n.s.
> 4 active joints	36 (59%)	20 (33%)	18 (30%)	n.s.
> 4 limited joints	26 (43%)	18 (30%)	33 (54%)	<0.001

* Values are given in median and interquartile range (IQR 25-75%) or number and percentage as indicated
† Limited joints = joints with limitation in range of motion (17)
‡ Physician's global assessment of disease activity score (PGAS): 0 = none; 1+ = very low; 2+ = low; 3+ = moderate; 4+ = active; 5+ = very active

Joint surgery was performed in 8 patients (13%): synovectomy in 4 (ankles, knees, wrist), hip arthrotomy in 1, hip replacement in 2 (bilateral in 1), finger joint prostheses in 1, ankle arthrodeses in 1, corrective surgery in hand, foot, or maxilla in 3 patients. All aforementioned outcome descriptions were comparable in both treatment groups.

Long-term outcome of combined trial groups. In the outcome assessment, active joints were present in 74% of the patients, including 30% with active polyarthritis. Compared to the end of the trial, follow up of both groups combined showed a significant increase in joint limitation but otherwise a more or less stable situation in clinical parameters and acute phase reactants (Table 2). The median C-HAQ for the whole group was 0.25 (range 0-2). None to mild disability was reported by 74% of the patients, moderate disability by 20% and severe disability by 6% of the patients.

Table 3. DMARD use in the follow-up period from trial inclusion to review for follow-up of 61 patients with juvenile idiopathic arthritis who participated in a placebo-controlled sulfasalazine-trial*

Variable	Placebo group n = 29	Sulfasalazine group n = 32	*P*-value
Medication use in follow-up period:			
No. of DMARDS used in follow-up period, median (range)	2 (0-5)	1.5 (1-5)	n.s.
No. (%) of patients with SSZ use	24 (83)	32 (100)	0.02
Duration of SSZ use in years, median (IQR)	5.2 (2.1-8.0)	2.5 (0.5-4.9)	0.02
No. (%) of patients with MTX use	16 (55)	15 (47)	n.s.
Duration of MTX use in years, median (IQR)	4.0 (3.0-5.8)	3.0 (1.5-5.0)	n.s.
No. (%) of patients with prednisone use	3 (10)	2 (6)	n.s.
Duration of prednisone use in years, median (IQR)	2.0 (2.0-6.0)	0.9 (0.3-1.5)	n.s.
No. (%) of patients with intramuscular gold use	3 (10)	5 (16)	n.s.
Duration of intramuscular gold use in years, median (IQR)	4.0 (1.5-7.0)	1.5 (0.5-2.8)	n.s.
No. (%) of patients with hydroxychloroquine use	0	3 (9)	-
Duration of hydroxychloroquine use in years, median (IQR)	0	6.2 (0.1-6.5)	-
No. of patients with use of other DMARDs†	1	1	-
Current medication use:			
No. (%) of patients with current DMARD use	21 (72)	17 (53)	n.s.
No. of patients with current use of:			
SSZ monotherapy	10	4	-
SSZ in combination treatment	4 MTX	2 MTX	-
MTX monotherapy	6	8	-
MTX in combination treatment	4 SSZ, 1 prednisone	2 SSZ, 1 HCQ	-
Hydroxychloroquine	0	1	-
Anti-tumor necrosis factor	0	1	-

* SSZ = sulfasalazine, MTX = methotrexate, HCQ = hydroxychloroquine PLAC = Placebo
† Other DMARDs included: in 1 PLAC patient: 9 months treatment with cyclosporine and an autologous bone marrow transplantation (27); respectively in 1 SSZ patient: 6 months of leflunamide treatment followed by recent introduction of anti-TNF-treatment.

Table 4. Comparison of outcome variables of placebo and sulfasalazine allocated patients who participated in a randomized placebo-controlled sulfasalazine trial and long-term follow-up study*

Variables	Trial baseline		End of trial (24 weeks)		Follow-up (median 9 years)	
	PLAC group n = 29	SSZ group n = 32	PLAC group n = 29	SSZ group n = 32	PLAC group n = 29	SSZ group n = 32
Active joints (range 0-71)	6 (3-11)	5 (2-11)	4 (1-11)	1*** (0-5)	4 (1-7)	2** (0-3)
Limited joints (range 0-67)	4 (1-8)	3 (1-6)	3.5 (1-6)	2 (1-4)	7 (3-13)	4 (1-12)
Physician's score of disease activity (PGAS range 0-5)	4 (3-4)	3 (2-4)	3 (2-3.5)	1**** (0-2)	2 (1-3)	1.5 (0-2)
Erythrocyte sedimentation rate mm/hour	35 (11-54)	25 (12-38)	14 (8-29)	9 (6-15)	10 (7-26)	6 (4-18)
Physician's VAS disease activity (range 0 – 100)	n.a.	n.a.	n.a.	n.a.	18 (3-31)	7 (0-16)
Patient's VAS overall well-being (range 0 – 100)	n.a.	n.a.	n.a.	n.a.	13 (2-55)	2** (1-28)
C-HAQ score (range 0-3)	n.a.	n.a.	n.a.	n.a.	0.25 (0-2)	0.25 (0-1.8)
No. (%) of patients improved according to the ACR Pediatric 30 definition†	n.a.	n.a.	6 (21)	18 (56)§****	5 (17)	15 (47)**
No. (%) of patients in remission at follow-up‡	n.a.	n.a.	n.a.	n.a.	1 (3)	8 (25)**
No. (%) of patients with episodes of remission between SSZ trial inclusion and follow-up	n.a.	n.a.	n.a.	n.a.	4 (14)	13 (41)**
Duration of episodes of remission in years	n.a.	n.a.	n.a.	n.a.	3.5 (2.3-6.3)	5.0** (3.5-7.0)

Footnotes **Table 4**.
* Values are median and interquartile range (IQR), unless otherwise indicated. PLAC = placebo, SSZ = sulfasalazine, N.a. = not applicable. C-HAQ = child health assessment questionnaire (CHAQ) and health assessment questionnaire (HAQ) results combined.
Physician's global assessment of disease activity score (PGAS): 0 = none; 1+ = very low; 2+ = low; 3+ = moderate; 4+ = active; 5+ = very active; Physicians' visual analogue scale (VAS) disease activity (anchoring words 0= inactive, 100 = severe) and patients' VAS overall-well-being (anchoring words 0 = very well; 100 = very poor)
† Improvement according to the ACR Pediatric 30 (ACR Pedi 30) definition (25). Variables included were: (1) number of active joints, (2) number of limited joints, (3) physicians' global assessment of disease activity, and (4) erythrocyte sedimentation rate. Patients were classified as improved when they showed at least 30% improvement in 3 of 4 aforementioned variables, and not one of the variables could be worsened by more than 30%
‡ Remission was defined as clinical remission off anti-arthritis and anti-uveitis medication for at least 12 months (24); episodes of remission were defined as the presence of episodes of disease remission off medication during the disease course between trial inclusion and follow-up.
, *, ****, *P* values of <0.05, <0.01 and <0.001 for the differences in outcome scores between the treatment groups.
§ Of the 18 SSZ patients who were improved according to the ACR Pedi 30 at the end of the trial, 11 (73%) remained 'improved' at follow-up; of the 6 PLAC patients who were improved at the end of the trial, none remained improved at follow-up ($P < 0.001$).

Follow up of treatment per trial group. Thirty-two (52%) of the 61 study participants available for follow-up had been randomized to SSZ and 29 (48%) to PLAC. Treatment before SSZ-trial inclusion was comparable, as reported previously (13). At the end of the trial, 23 (72%) of the SSZ patients continued SSZ treatment and 6 (19%) switched to other DMARDs (total on DMARDs 91%; Table 3). At follow up, 17 patients of the SSZ group (53%) were on DMARDs, including 4 still on SSZ. The median duration of SSZ treatment of SSZ patients (including the trial period) was 2.5 years (IQR 0.5-4.9). In due course, 16 (50%) SSZ patients switched to other DMARD treatment, including methotrexate (MTX) in 15 (47%). Median duration of MTX treatment of those SSZ patients was 3.0 (IQR 1.5-5.0) years. Median number of DMARDs used in the follow-up period (from SSZ-trial inclusion to review for follow-up) for SSZ patients was 1.5 (range 1-5).

In the PLAC group, 24 of 29 patients started SSZ (83%), and 3 another DMARD (total on DMARDs: 93%; Table 3). At follow-up 21 patients of the PLAC group (72%) were on DMARDs, including 4 still on SSZ. The median duration of SSZ treatment in the PLAC group was significantly *longer* than in the SSZ group: 5.2 years (IQR 2.1-8.0; $P = 0.02$). A similar (nonsignificant) trend was seen for most other DMARDs. In due course 64% of the PLAC group switched to other DMARDs, including MTX in 16 (55%) of the patients. The median duration of MTX treatment of those PLAC patients was 4.0 (IQR 3.0-5.8) years. The median number of DMARDs used in the follow-up period by PLAC patients was 2 (range 0-5).

Prednisone was rarely prescribed. During follow-up, one PLAC and 3 SSZ patients experienced a (temporary) remission off medication after an adverse event on SSZ treatment: 1 patient with bruising, 1 with leucopenia, fever and rash, and 2 with dysimmunoglobulinaemia (28). Intra-articular steroid treatment was used in 52% of the PLAC patients respectively 56% of the SSZ patients.

Long-term outcome per trial group. At follow-up most outcome scores were much (>50%) better in the SSZ group than in the PLAC group, except for identical results in the C-HAQ (Table 4). These differences were significant for the number of active joints, patients' overall well-being, ACR Pedi 30, patients with episodes of clinical remission off medication, duration of episodes of clinical remission off medication, and patients in clinical remission off medication at the time of the follow up assessment. Results were unchanged when 10 RF positive JIA subtype patients were excluded from analyses (results not shown).

ACR Pedi 30 improvement during the SSZ trial was significantly better sustained in the SSZ group. At follow-up, 15 of the SSZ patients (47%) classified as ACR Pedi 30 responder compared to 5 of the PLAC patients ($P = 0.02$): 11 of these SSZ patients (73%) were already classified as ACR Pedi 30 responders at the end of the SSZ trial, and remained 'improved', compared to none of the PLAC patients ($P < 0.0001$). The 11 SSZ patients that remained 'improved' were classified in the following JIA subtypes: oligo-persistent (3 patients), oligo-extended (4 patients), rheumatoid factor positive (1 patient), enthesitis related arthritis (1 patient), arthritis and psoriasis (1 patient), and other arthritis (1 patient).

Compliance with DMARD treatment. In the follow-up period, 24 (41%) of the 59 patients (including 14 (48%) PLAC and 10 (32%) SSZ patients; $P = 0.18$) who were prescribed DMARDs by their treating physician, reported prolonged discontinuation of taking these DMARDs due to severe resentment against medication use. The outcome of these patients differed considerably from the patients reporting good compliance with the treatment regimen. Patients reporting good compliance showed significantly better scores for all joint modalities (swelling, pain, LOM, active), physicians' disease activity scores, patients' VAS pain and patients' VAS overall well-being scores (results not shown). Compliant patients also experienced a higher number of episodes of remission off medication ($P = 0.007$), a lower number of operations ($P = 0.03$) and showed more often inactive disease at review for follow-up ($P < 0.0001$).

Potential confounders. We performed additional explanatory analyses to detect potential confounders in the relationship between group allocation in the original trial and outcome. For this analyses, good outcome was defined as PGAS ≤ 2 or the presence of ACR Pedi 30 at follow-up. In univariate analysis, PGAS good outcome was associated with allocation to the SSZ group (OR 3.5 (95 CI 1.1-11.1), $P = 0.03$), male sex (OR 6.4 (1.3-31.0), $P = 0.01$), and compliance (OR 4.3 (1.4-13.5), $P = 0.01$). In multivariate analysis, male sex (OR 6.0 (1.2-31.0), $P = 0.03$) and compliance (OR 4.1 (1.2-13.6), $P = 0.02$) remained significant factors. Adjusted for gender and compliance, the odds for PGAS good outcome in the SSZ group were 3.3 times higher (0.6-12.5, $P = 0.06$) than the odds for the PLAC group.

In univariate analysis, allocation to SSZ (OR 4.2 (95% CI 1.3-13.9), $P = 0.02$) and compliance with DMARD therapy (OR 3.8 (1.1-13.4), $P = 0.03$) positively correlated with ACR Pedi 30 improvement at follow-up. Duration of MTX treatment (OR 0.7 (0.5-0.97), $P = 0.02$) and number of DMARDs used during the follow-up period (OR 0.4 (0.2-0.9); $P = 0.03$) correlated

negatively with ACR Pedi 30 improvement. In multivariate analysis, only compliance remained a significant factor. Adjusted for compliance, the odds for ACR Pedi good outcome were 4.2 times higher (95% CI 1.3-14.3, $P = 0.02$) in the SSZ group than the odds for the PLAC group. Adjustment in addition for duration of MTX treatment and number of DMARDs used during the follow up period changed the odds ratio for presence of ACR Pedi good outcome in the SSZ group to 4.7 (95% CI 1.2-18.3, $P = 0.03$).

The study group was too small to reliably analyze the effects across JIA onset subtypes. Nevertheless, the long-term advantage of SSZ over PLAC was maintained in both oligoarticular-onset (n = 33) and polyarticular-onset (n = 28) subgroups, although statistical significance was lost in the latter (data not shown).

DISCUSSION

The findings presented here demonstrate that in relatively early JIA, a 6-month head start in the initiation of SSZ therapy leads to a better outcome 9 years later. At review for follow-up, patients in the SSZ group were in much better health than those in the PLAC group: numerical differences were apparent in almost all comparisons, and many of these were statistically significant. We believe this is the first strong evidence to support early intervention with a DMARD in active JIA. Patients' compliance with prescribed DMARD treatment appeared another important factor related to presence of active disease and overall outcome.

Almost all measures studied, point to a lower level of disease activity over time in the SSZ group. It is of note that post trial treatment appeared less intensive in the SSZ group as evidenced by the lower number of used DMARDs, the lower median duration of use of different DMARDs, and the lower number of patients with current DMARD use at follow-up. This suggests that SSZ patients were in better condition, and needed less treatment to maintain good disease status. This would also explain the results of the confounder analysis, where a longer duration of MTX therapy correlated with less likelihood of ACR Pedi 30 improvement. Our trial showed that SSZ was effective in suppressing disease activity and retarding radiological progression in JIA (13, 29). These observations support the concept that the level of disease activity is set at an early active stage of the disease, and that pharmacological resetting of the disease process is easiest to achieve within a narrow time frame. This so-called "window of opportunity" has been observed in several studies in adults (30-34) but not yet in JIA. Notably, we observed this window even though SSZ could be termed 'moderately active' and its onset late by current standards (35,36).

Despite these promising results, and despite the low median C-HAQ values in both groups, the range of C-HAQ values, the presence of active disease and the increase in limited joints at follow up points to substantial room for improvement in JIA care. For the nineties, treatment of the study participants can be qualified as intensive compared to other JIA outcome studies (2,4). Probably the trial cohort preferentially included severe cases of oligoarticular- and polyarticular-onset JIA patients. Another explanation for persistent disease is the impressive

non-compliance we were able to document. Compliance is known to be a precarious issue, especially in adolescents with chronic disease (37). Results of our study show a clear relation between therapy compliance and a better disease outcome as reflected in joint scores, patients' scores and probability of surgical intervention. The results of this study suggest unrelenting attention to this issue is needed in daily practice.

This study has limitations. Although its start as a trial suggests equal prognosis of treatment groups at baseline, the small group size, the uncontrolled treatment strategy and retrospective data collection all increase the chance of bias. Exploratory analyses increase the chance of type 1 errors. Nevertheless, from the additional confounder analyses it appears unlikely that the better outcome of SSZ patients is due to differences in patient characteristics or consecutive DMARD therapy. We cannot completely rule out that despite stratification per JIA onset subtype and randomization for treatment assignment, patients with more progressive disease were unequally divided over the treatment arms. Prospective controlled studies are preferable to determine the influence of timing and sequence of specific DMARD treatment in different subtypes of JIA, but it is very hard to organize these type of studies.

In summary, this is the first study to show that effective suppression of disease activity by SSZ treatment early in an active phase of disease in oligoarticular- and polyarticular-onset JIA patients has beneficial effects that persist for many years. This study supports the assumption that early institution of aggressive antirheumatic treatment relates to a better long-term outcome for JIA patients. In addition, patients' treatment compliance deserves attention. Future studies have to elaborate which antirheumatic treatment strategy is most effective in suppression of disease activity and prevention of long-term joint damage.

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Chapter 8

Summary and discussion

SUMMARY

In this thesis we describe the clinical and radiological observations of oligoarticular and polyarticular onset juvenile idiopathic arthritis (JIA) patients who participated in a multicenter randomized placebo-controlled sulfasalazine (SSZ) trial of 24 weeks' duration that was performed in the period 1992-1994 in the Netherlands. This study was a cooperative effort of the Dutch Juvenile Idiopathic Arthritis Study Group. In addition, we present the long-term outcome of the trial participants, who were reviewed between 2001-2003.

In order to analyze the radiological observations made during the SSZ-trial, we developed the first standardized radiological assessment score to be used as outcome measure in clinical trials in JIA, 'the Dijkstra score', which is also presented in this thesis.

Chapter 1

General introduction. The introduction starts with an extensive description of the nomenclature and classification of chronic arthritis in childhood (demonstrated in Table 1 of that chapter), followed by current perspectives on etiology and pathophysiology of JIA. The chapter continues with a section about the pharmacology of SSZ with a focus on anti-inflammatory and immunomodulatory properties observed in laboratory research. Subsequently, attention is given to the evolution of treatment strategies of JIA since the 1990s, as there has been a change in attitude towards the timing of introduction of DMARD therapy. This subject is followed by a brief history of the use of SSZ in RA and JIA, and an overview of efficacy studies of SSZ treatment in JIA is presented in Table 2. Also, other controlled JIA treatment studies performed during the passed 15 years are evaluated. The development of outcome measures to be applied in clinical trials in JIA is explained and the variables of the current definition of improvement (American College of Rheumatology Pediatric 30 response; ACR Pedi 30) are summarized in Table 3. Special attention is given to the radiological assessment in JIA; the challenges of developing a scoring system for use in clinical trials are outlined. The introduction ends with a summary of recent findings concerning disease course, outcome and outcome related factors.

Chapter 2

Sulfasalazine trial in patients with juvenile idiopathic arthritis. Between 1992 and 1994, we conducted the first trial to assess the efficacy, tolerability and safety of sulfasalazine (SSZ) in children with oligoarticular and polyarticular JIA. This 24 week, multicenter, double-blind randomized placebo controlled SSZ-trial included 37 oligoarticular and 32 polyarticular-onset JIA patients. All patients had at least one joint with active arthritis and an indication to receive DMARD therapy according to their treating physician. Patients were treated with SSZ 50 mg/kg/day (maximum 2000 mg/day) in 2 dosages or placebo (PLAC). The efficacy variables were joint scores, physicians', parents' and patients' overall assessments and laboratory parameters of inflammation.

Of the 69 patients enrolled, 75% completed the trial; 18% withdrew from the PLAC group, mainly for inefficacy, and 31% from the SSZ group, including 29% because of adverse events. Data were analyzed based on the intention-to-treat principle with the last observation carried forward in case of missing values. The results showed that in all outcome assessments SSZ randomized patients had better scores compared to PLAC patients. A difference in treatment effect already occurred within 12 weeks of trial participation and thereafter a lower disease activity level was maintained in the SSZ group. At the end of the trial, the differences between the treatment groups were significant for the number of active joints, overall articular severity score (including scores for swelling, limitation of motion, and pain, and scores for severity of these items), all global assessments by the patients, parents and physicians, laboratory parameters of inflammation, and response according to the preliminary definition of improvement (1).

Adverse events leading to discontinuation of treatment also occurred significantly more in the SSZ group; however, in all instances, these events were transient or reversible upon cessation of treatment. The adverse events mainly consisted of gastrointestinal symptoms, skin rashes and laboratory disorders. In one patient there was a hypersensitivity reaction in the third week of therapy.

We concluded that SSZ was effective and safe in the treatment of children with oligo- and polyarticular-onset JIA, although it was not well tolerated in one-third of the patients.

Chapter 3.

Effects of sulfasalazine treatment on serum immunoglobulin levels. In this study, we elaborate on one of the observed adverse events of SSZ treatment during the trial, the occurrence of low serum immunoglobulin levels, and question whether measurement of immunoglobulin levels should be routinely performed during SSZ treatment. We describe a case series of 6 children with oligo- or polyarticular-onset JIA who developed dysimmunoglobulinemia (lowering of individual immunoglobulin (Ig) levels), including IgA, IgM, IgG, and IgG2, during SSZ treatment. None of these children showed symptoms of this adverse event, in particular none developed severe infections. All regained normal serum immunoglobulin levels after cessation of treatment, although during the follow-up period of 4-6 years, 2 patients showed spontaneous changes in their immunoglobulin repertoire: one developed again a dysimmunoglobulinemia and another one diabetes mellitus. The development of low serum immunoglobulin levels has also occasionally been observed in RA patients treated with SSZ. The changes in serum immunoglobulin levels were attributed to anti-inflammatory and immunomodulatory properties of SSZ. Beside, patients with JIA may be more prone to development of this type of adverse event because they show more immunoregulatory abnormalities compared to healthy children.

Based on these case reports and a review of the literature, we advocate monitoring of serum immunoglobulin levels while on SSZ treatment.

Chapter 4.

Anti-cyclic citrullinated peptide (anti-CCP) antibodies in children with juvenile idiopathic arthritis. In adults with RA, the presence of anti-CCP was shown to be very specific for the diagnosis of RA and appeared of value in predicting a more destructive disease course. In line with these findings, we questioned whether anti-CCP could be detected in sera of JIA patients to support the diagnosis and if anti-CCP could also be used in JIA to identify patients with a more severe destructive course of disease.

We therefore analyzed 100 serum samples of 71 JIA patients taken at different time points in their disease course with a commercially available anti-CCP1 ELISA for the presence of anti-CCP. Correlations between anti-CCP, disease characteristics, medication and radiological damage (presence of joint space narrowing and/or erosions) were determined. The serum samples came from patients of all 7 different JIA subtypes (median age 10.5, range 2-20 years; disease duration median 24, range 3-245 months).

Anti-CCP tested positive in 8 out of 11 (73%) IgM-RF positive JIA patients and in 2 (3%) of the other JIA subtype patients ($P < 0.0001$). The disease duration, medication, and anti nuclear antibody positivity did not differ significantly between the anti-CCP positive and negative patients. Testing of follow-up samples showed almost identical anti-CCP results. All 11 IgM-RF positive JIA patients had radiological damage ($P < 0.001$) and the 2 positive anti-CCP patients without IgM-RF had no radiological abnormalities. Of the anti-CCP positive patients, 80% had radiological damage, resulting in a significant difference between anti-CCP positive and anti-CCP negative patients with an odds ratio of 12.7; however, after correction for the correlation between IgM-RF and anti-CCP positivity, the odds ratio was no longer significant.

We concluded that the high prevalence of anti-CCP antibodies in IgM-RF positive JIA patients showed that anti-CCP is associated with a specific subgroup of JIA patients, but is not supportive for the diagnosis of JIA in general. Further follow-up studies are required to establish more firmly whether the presence of anti-CCP antibodies in JIA patients predicts the development of a disease course as in adult RA and predicts a more destructive disease course.

Chapter 5.

Radiologic features in juvenile idiopathic arthritis: a first step in the development of a standardized assessment method. In Chapter 5 and 6 we describe the development of a standardized radiological assessment score to be used in the evaluation in clinical trials in JIA. Although there are several advanced scoring systems available for RA, these cannot be used in JIA because of the differences in radiological manifestations of both diseases. In this first radiological study, the objectives were to describe the radiological features of patients with JIA in a standardized manner, to test the reliability and feasibility of this description, and to correlate these features with clinical signs.

For the purpose of this study, we used the radiographs and clinical data from the 24 week, multicenter, placebo-controlled SSZ trial that is presented in Chapter 2. All trial entry radiographs (taken from the clinically involved joints and contralateral joints) were scored (in consensus by skeletal radiologist PD and pediatric rheumatologist MvR) for the presence

or absence of a comprehensive spectrum of radiological manifestations of JIA: swelling, osteopenia, joint space narrowing, growth abnormalities, subchondral bone cysts, erosions, and malalignment. All 68 clinically involved joints were included in the maximum of 19 radiographed joints (or joint groups) per patient. Data from 67 of 69 patients were analyzed. The mean age of the patients was 9.1 years (range 2.5-17.6), the median disease duration 24 months (range 5-176) and the mean number of radiographed joints per patient was 7 (range 2-15).

The radiological assessment showed that knees, hands, ankles and feet were most frequently affected. Radiographic abnormalities in at least one joint were observed in 87% of the patients. These abnormalities consisted of soft tissue swelling in 63% of the patients, growth disturbances in 48%, joint space narrowing in 28% and erosions in 15% of the patients, respectively. In total, half of the radiographs of the clinically involved joints showed radiological abnormalities, including two-third of the clinically affected hands and knees. Notably, a relatively high proportion of hand and foot radiographs (36% and 39%, respectively) showed abnormalities without distinct clinical symptoms, while this proportion was lower in the other joints (e.g. knee 23%, ankle 10%).

Additional analysis showed that there was a good correlation between the overall articular (clinical) severity of a joint and the presence of radiological abnormalities. Patients with IgM-RF or HLA-B27 positivity had radiological abnormalities significantly more often than the other patients. In general, the reproducibility of the radiologic scoring was estimated as good: mean kappa coefficient of 0.74 (range 0.40-0.86), although there were scoring discrepancies for swelling, osteopenia, and growth abnormalities. The scoring took 10-20 minutes per patient.

We concluded that our model of describing and scoring radiological abnormalities in JIA was feasible, mostly reproducible, correlated well with the overall articular severity score and added substantial new information not available in clinical examination.

Chapter 6.

Development of a standardized method of assessment of radiographs and radiographic change in juvenile idiopathic arthritis. In Chapter 6, we continue with the development of a radiological assessment score and evaluate the sensitivity to change of the radiologic assessment method, hereafter named the *Dijkstra score*, and describe the development of a numeric composite score and progressor classification scheme to apply in JIA trials. For the purpose of this study, we used the radiographs of the SSZ-trial participants again. These included 418 sets of radiographs of the clinically involved and contralateral joints at study entry and at 6 months follow-up from 66 patients. We assessed these radiographs for the absence or presence of radiologic abnormalities according to the Dijkstra score as described above.

Subsequently, for a further *standardized numeric* evaluation of the data, we defined the Dijkstra composite scores for each radiographed joint as follows: the *Dijkstra inflammation (DI) score* (range 0-2) is the summation of scores for swelling (0-1) and osteopenia (0-1); the

Dijkstra damage (DD) score (range 0-3): is the summation of scores for joint space narrowing (0-1), bone cysts (0-1), and erosions (0-1); and the *Dijkstra growth (DG) score* is the score for growth abnormalities (range 0-1). The DI, DD, and DG scores were calculated at study entry and at follow-up for each radiographed joint and for each patient, and the values at both time points were compared. An increase in any of the Dijkstra composite scores was deemed to indicate joint deterioration, while a decrease reflected improvement. The malalignment sign was excluded from analysis, since its prevalence was too low to generate useful data.

Joint damage was subsequently *categorized as progressive* when either the DD or the DG scores in a joint increased. The disease course in all other joints was considered to be nonprogressive. Scores were evaluated among all radiographs, a *standard set of films* (hand, foot, and knee) and per patient. All scores were used to explore differences between the 2 treatment groups (PLAC - SSZ).

The results showed that these definitions worked well in this trial dataset. Of the 66 JIA patients, 12% had normal radiographic findings throughout follow-up, 27% showed abnormalities at some sites without change, and 61% showed change in at least 1 site. Changes in the DI, DG, and DD scores varied considerably per type of joint and occurred most frequently in the joints of the standard set. DI and DG scores changed most often in the knees, whereas DD scores changed primarily in the hands and feet. The disease course was defined as progressive in 8% of the joints.

A comparison of radiographs from the SSZ-treated patients with films of the PLAC group showed significant differences in outcome: films of the SSZ group showed significantly less deterioration in the DD scores, and the disease course on films was classified as non-progressive more often in the SSZ group. If progressors were defined as patients who had at least one radiograph showing progression, significantly more PLAC patients were considered progressors.

We concluded that with this study the initial validation phase of the Dijkstra score was complete. In this trial data set, the Dijkstra composite score and the resulting progressor classification system appeared comprehensive and feasible tools that were sensitive to change and were able to discriminate between clinical situations. To further validate the scores they should now be tested by other investigators and in other datasets.

Chapter 7.

Long-term outcome of the sulfasalazine trial participants. In the final study included in this thesis, we describe the long-term outcome of the SSZ-trial participants and evaluate if the benefits of SSZ allocation during the SSZ-trial were sustained over time. For this follow-up study, we reviewed 32 SSZ and 29 PLAC patients (90% of all patients) between 2001 and 2003, at median 9 years after trial participation. The median age was 18 years (range 10-25) and disease duration 11 years (range 8-23). During the assessment variables of the ACR Pedi 30 were obtained. Disease course and treatment related data were retrieved from medical records. The outcome results were compared between PLAC and SSZ allocated patients.

After the SSZ-trial, patients had been routinely followed in rheumatology referral centers, and treated at the discretion of the attending physician. Almost all patients continued or

started DMARDs (SSZ group 91%, PLAC group 93%; SSZ treatment in about 80%). DMARD treatment was less intensive in the SSZ group as evidenced by a significantly shorter duration of SSZ use (median 2.5 vs. 5.2 years; $P = 0.02$), and a trend towards lower percentage of methotrexate users, median duration of methotrexate use, number of used DMARDs, duration of use of different other DMARDs, and percentage of patients on current DMARD treatment. Prednisone was rarely used. More than one-third of patients reported long periods of noncompliance with DMARD treatment in both groups.

At follow up, most patients (74%) had active joints and 30% showed active polyarthritis. Despite lower treatment intensity, almost all outcome scores were much better for SSZ than for PLAC patients. Differences were significant for the number of active joints, patients' overall well-being, number of patients experiencing clinical remission off medication, patients in remission or ACR Pedi 30 responder at follow-up, and duration of remission episodes. In additional exploratory analyses, DMARD treatment compliance was positively correlated with an ACR Pedi 30 response (odds ratio 3.8, 95% confidence interval (CI) 1.1-13.4; $P = 0.03$). Adjusted for compliance, a SSZ patient was 4.2 times as likely as a PLAC patient to be an ACR Pedi 30 responder at follow-up (95% CI 1.3-14.3; $P = 0.02$).

We concluded from this long-term follow-up study that effective suppression of disease activity by SSZ treatment early in active disease in JIA patients has beneficial effects that persist for many years. And given these results, compliance with DMARD treatment deserves serious attention.

GENERAL DISCUSSION

This thesis shows that SSZ is more effective than placebo in suppressing disease activity and retarding radiological progression in children with oligoarticular and polyarticular JIA. It also shows that the benefits of SSZ allocation are sustained over many years, despite more intensive treatment in the former placebo group. These observations support early intervention with DMARD in active JIA. Perhaps self-evident, but important to document as was done in the follow-up study, is that good DMARD therapy compliance leads to a better outcome.

Since the SSZ-trial, 3 other drugs were shown to be effective in JIA in randomized controlled trials: first methotrexate (MTX) (2-4), followed by etanercept (5) and most recently leflunomide (6). Since the introduction of MTX in treatment of JIA, its efficacy and toxicity have been widely studied. Because of the good efficacy of MTX, in combination with its low toxicity and convenient dosing, MTX has become the anchor drug in the management of JIA (7). The introduction of anti-tumor necrosis factor (TNF) treatment has improved the therapeutic options of patients with DMARD resistant JIA dramatically; however, safety issues and high costs limit its use (7-9). Despite the progress made, the total number of trials in JIA remains low compared to RA.

Apart from the SSZ-trial, efficacy of SSZ treatment in JIA has been confirmed in other, mostly uncontrolled, studies (reviewed in the General Introduction of this thesis). One of

the recurrent issues in discussions about treatment effects of SSZ is whether SSZ has more therapeutic benefits in one of the JIA subgroups. It is often suggested that SSZ is most effective in oligoarticular onset and enthesitis related arthritis (ERA) patients (10-12). So far there is insufficient data to resolve this issue (13). Our SSZ trial was not designed or powered to answer this question, but only to investigate whether SSZ was effective in oligoarticular and polyarticular onset JIA.

Compared to the other drugs with proven efficacy in JIA treatment (MTX, etanercept and leflunomide), SSZ appears a 'moderately active' drug as reflected in ACR Pedi 30 response rates reported in the randomized controlled trials (summarized in Table 1 of this chapter) (3-6,14). The interpretation of these data requires some caution with respect to differences in patient characteristics, inclusion of a functional measure, disease severity and disease duration (e.g. MTX / leflunomide comparative trial median disease duration 4 months vs. etanercept trial mean disease duration more than 5 years). Nevertheless, the ACR Pedi 30 response rates of high dose MTX in the MTX / leflunomide study (89%) and etanercept (74%) are impressive compared with the rates of SSZ (44%) and medium dose of oral MTX (48%).

Although SSZ is frequently used in combination with MTX in JIA treatment (15,16, SSZ-trial follow-up study, this thesis), there are no studies that report effectiveness of this treatment strategy in JIA. Several studies performed in RA suggest that the combination of SSZ and MTX has no additive therapeutic benefit and that adding is not better than switching (17,18). The effects of combination therapy appear to be different when the combination of SSZ, MTX and prednisone (COBRA regimen)(19) is initiated early in the disease course of RA patients: results of the COBRA and BeSt study (20) demonstrate that, in early RA, the COBRA regimen (step-down combination of therapy with prednisone, MTX and SSZ) is more effective in suppressing disease activity and retarding radiological progression in comparison with either monotherapy or step-up combination therapy; and equivalent to the combination of high-dose MTX and infliximab (19,20). In addition, results of a 5-year follow-up study show that an initial 6 months of the COBRA regimen result in a sustained suppression rate of radiological progression (21). The better long-term outcome of the patients allocated to SSZ during the SSZ-trial (as described in this thesis) are consistent with the findings of the COBRA trial; however, whether the radiologically observed benefits in the SSZ-group of the SSZ-trial also are sustained, remains to be established.

One of the disadvantages of SSZ treatment is the frequent occurrence of adverse events. All studies on SSZ treatment show that the side effects are generally mild and resolve when the medication is stopped (13,14). Hypersensitivity reactions do occur and in systemic JIA patients more severe toxicity may develop (10,15,22). There are no reported malignancies or deaths attributable to SSZ exposure in children. Regular laboratory monitoring is required especially in the first months of SSZ therapy and patients and parents need to be well instructed about the symptoms of adverse events. Together with the divided daily doses and the limited availability of a liquid form of the drug, these impracticalities have set bounds to the use of SSZ.

Table 1. Controlled clinical trials of disease modifying antirheumatic drugs in juvenile idiopathic arthritis reporting ACR Pediatric 30 response*

Source	Van Rossum et al. (14)	Woo et al. (3)	Lovell et al. (5)	Ruperto et al. (4)	Silverman et al. (6)
Study drug	SSZ 50 mg/kg/day maximum 2 g per day versus PLAC	Oral MTX 15-20 mg/m^2 per week versus PLAC	Etanercept open label followed by double-blind Etanercept versus PLAC	Parenteral MTX 15 mg/m^2 per week versus Parenteral MTX 30 mg/m^2 per week	LEFLU 10 mg every other day to 20 mg per day versus MTX 0.5 mg/kg per week
Study type	Randomized, double-blind, multicenter	Randomized, double-blind, cross-over, multicenter	Open label followed by randomized double-blind withdrawal, multicenter	Randomized, open international	Randomized, double-blind, multicenter
Patient number	69	88	69 open label †, 51 double-blind	80‡	94
Length of treatment	24 weeks	16 weeks	12 weeks open label and 16 weeks double-blind	26 weeks	16 weeks
Type of arthritis	All subtypes JIA excluding systemic patients	Extended oligoarticular JIA and systemic JIA with polyarthritis	JRA with polyarthritis course including RF positive patients	JRA with polyarthritis course excluding RF positive patients	JRA with polyarthritis course including RF positive patients
Systemic onset patients %	Not included	Systemic 51	Systemic 32	Medium MTX 17 High MTX 15	LEFLU 2 MTX 0
Disease duration (years)	PLAC median 1.4 SSZ median 2.2	EOA mean 4.4 Systemic mean 2.8	Mean 5.9	Medium MTX mean 3.2 High MTX mean 2.6	LEFLU median 0.33 MTX median 0.33
Number of active joints mean ±SD	PLAC median 7 (IQR 3-12) SSZ median 5 (IQR 2-11)	EOA mean 16 ±13 Systemic mean 20 ± 19	Mean 28	Medium MTX mean 14.7 ± 9.2 High MTX mean 14.7 ± 9.5	LEFLU mean 14.4 ± 7.9 MTX mean 14.0 ± 9.9
Definition of response	ACR Pediatric 30§	ACR Pediatric 30§	ACR Pediatric 30	ACR Pediatric 30	ACR Pediatric 30
Responders / Flare %	PLAC 21 SSZ 44**	MTX systemic 25 MTX EOA 48** PLAC Systemic 16 PLAC EOA 18	Open label: Responders 74 Double-blind Flare: Etanercept 28¶** Placebo 81¶	Medium MTX 63 High MTX 58	LEFLU 68 MTX 89**
Non-completers %	PLAC 18 SSZ 31	EOA 5 Systemic 15	Open label 7 Double blind n.a.	Medium MTX 15 High MTX 28	LEFLU 11 MTX 6
Comments	IAC not allowed	IAC not allowed; MTX dose allowed to increase after 2 months	IAC not allowed	IAC not allowed	4% LEFLU and 9% MTX patients received IAC; LEFLU dose per weight; MTX maximum dose 25 mg/wk

Footnotes **Table 1.**
* JIA = juvenile idiopathic arthritis (40); JRA = juvenile rheumatoid arthritis (41); SSZ = sulfasalazine; PLAC = placebo; MTX = methotrexate; LEFLU = leflunomide; Medium MTX = medium dose parenteral MTX 15 mg/m2/week; high MTX = high dose parenteral MTX 30 mg/ m2/week; IAC = intra-articular steroids; IQR = interquartile range
RF = rheumatoid factor; juvenile idiopathic arthritis subtype classifications: systemic = systemic arthritis; EOA = extended oligoarticular arthritis; ACR Pediatric 30: American College of Rheumatology Pediatric 30 response criteria of improvement (1)
** significant positive effect
† 51 responders in a 12-week open phase were randomized from 69 patients
‡ 80 patients not responsive to oral MTX 10 mg/ m2/week (out of 595 patients)
§ without functional measure
¶ percent of patients who experienced arthritis flares

Assessment of radiographs to evaluate efficacy of JIA treatments has been hampered by the lack of availability of an established, generally accepted, validated scoring method for use in pediatric patients. As described in this thesis, we developed and validated the first standardized radiological assessment score to be used in trials of oligoarticular and polyarticular JIA. The Dijkstra score, Dijkstra composite score and progressor classification, have appeared feasible tools in the evaluation of the radiographs of the SSZ trial. The results show that SSZ is more effective than placebo in retarding radiological progression, which is in line with findings in adults (23,24). So far, we have not been able to evaluate the prognostic properties of the score; the radiographs of the participants of the SSZ-FU study may serve this purpose. The Dijkstra score needs further validation by other investigators and in other datasets.

Recent studies in RA underline the importance of inclusion of a radiological evaluation in trials as reliance on clinical measures only appeared insufficient to evaluate efficacy of treatment. Some drug (combinations) have demonstrated to be more effective in retarding radiological progression compared to other drugs that show similar benefit in suppressing disease activity (20,25-27). The inclusion of a validated and generally accepted standardized radiological assessment score in therapeutical studies in JIA is therefore essential.

At present, the effectiveness of treatment in JIA is still disappointing. The lack of knowledge about the etiology and pathophysiology of JIA, the variability of the disease, and the uncertainty about the mechanism of action of the drugs used, hinder the development of a consistent approach to the therapeutical management of JIA. The goals of JIA treatment are straightforward: to ameliorate acute symptoms, suppress disease activity to a quiescent state, induce remission and improve outcome by preventing joint damage. So far, there are no therapies that have demonstrated these results. Recent studies, including the SSZ-trial follow-up study, have shown that the majority of JIA patients enter adulthood with active disease and that patients move back and forth between active and inactive disease during the disease course (28,29, this thesis). Another recent follow-up study revealed that the majority of patients with extended oligoarthritis, polyarthritis, and systemic arthritis spent nearly two third of their time with active disease (29). Taken together, these data demonstrate that disease activity is not adequately suppressed in many JIA patients.

The results of the SSZ-trial follow-up study show evidence for the concept that there is a 'window of opportunity' early in the disease course during which the treatment is significantly more effective than later in the disease course (30,31). This leads to a treatment strategy of a quick and complete suppression of disease activity, so as to prevent or minimize damage to the joints and to modify the development of an irreversible self-perpetuating inflammatory process.

Although the SSZ-trial results support the early use of SSZ for oligoarticular and polyarticular JIA treatment, the more prominent suppression of disease activity by high dose MTX (and etanercept) in polyarthritis patients (4-6) justifies the assumption that early initiation of these therapies may improve the long-term outcome even further. However, this assumption needs to be verified, as has been done for SSZ. In future JIA trials, efficacy and safety (short-term and long-term) of different treatment regimens including (combinations of) conventional DMARDs and anti-TNF therapy aimed at early and sustained suppression of disease activity need to be explored. Awaiting these results, a regimen including early use of SSZ remains a safe treatment option with proven long-term benefits.

At present, clinicians cannot accurately predict at diagnosis which JIA patients will have mild disease and which will develop a persistent more destructive disease course and thus require the most aggressive treatment. In the radiological evaluation study of the SSZ-trial participants (Chapter 5 of this thesis) the presence of IgM-RF or HLA-B27 were both independently associated with radiological damage. These associations have also been confirmed by others (32,33). The role of the presence of anti-CCP antibodies remains to be elucidated further in JIA, although it is most probable that their role is similar to that in adult RA, i.e. related to a more severe disease course (34-36, Chapter 4 of this thesis). Late referrals, young age at onset, long duration of elevated ESR, large number of affected joints at onset, and symmetric polyarthritis have also been identified as predictors of a more severe disease course (33,37-39). Within the coming years it is to be expected that additional serological parameters as well as genetic variations may identify those patients who will benefit most from early aggressive treatment.

Implications for future research. Treatment of JIA remains a challenge. Only a few randomized controlled trials have been performed in children with JIA. In addition, most studies only cover a relatively short period of time, whereas JIA is a chronic disease and patients may relapse while under DMARD treatment. This shortage of data leaves clinicians with little evidence upon which to base decisions regarding the best timing, dosages or combinations of medications to be used for fully effective treatment of JIA.

With cooperative efforts and development of protocols with different treatment strategies, containing (combinations of) conventional DMARDs and biologicals aimed at early and tight control of disease activity, the unraveling of these questions can proceed. In all study designs, the radiological evaluation of treatment efficacy is important, and now feasible. While performing these trials, unrelenting attention is required for the care and support of the patients who need to adhere to treatment for a long time.

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Chapter 9

Nederlandse samenvatting

SAMENVATTING

Dit proefschrift beschrijft de klinische en radiologische bevindingen bij oligoarticulaire en polyarticulaire juveniele idiopatische artritis (JIA, jeugdreuma) patiënten die deelnamen aan de eerste placebo-gecontroleerde sulfasalazine (SSZ) studie bij kinderen. Deze landelijke studie duurde 24 weken en werd verricht in de periode 1992-1994 door de Nederlandse Werkgroep voor Kinderreumatologie. Het antireumaticum SSZ werd onderzocht op werkzaamheid en veiligheid. Daarnaast wordt de lange termijn uitkomst van deelnemers aan deze studie beschreven op basis van vervolgonderzoek dat in de periode 2001-2003 plaatsvond. We analyseerden of patiënten die tijdens de SSZ studie placebo gebruikten in uitkomst verschilden van patiënten die met SSZ waren behandeld.

Om de radiologische bevindingen tijdens de SSZ-studie te beschrijven ontwikkelden we de eerste gestandaardiseerde radiologische scoringsmethode die gebruikt kan worden in studies bij kinderen met JIA.

In **Hoofdstuk 1** worden algemene aspecten van JIA behandeld. JIA is een verzamelnaam voor verschillende vormen van chronische artritis (gewrichtsontsteking) die ontstaan op de kinderleeftijd. Het is een klinische diagnose die wordt gesteld wanneer kinderen jonger dan 16 jaar een gewrichtsontsteking hebben die langer dan 6 weken duurt zonder dat er een andere aantoonbare oorzaak voor is gevonden. De term JIA omvat 7 verschillende subtypen: oligoarticulair (minder dan 5 ontstoken gewrichten), polyarticulair (5 of meer ontstoken gewrichten) serum reumafactor (RF) negatief, polyarticulair serum RF positief, artritis met enthesitis, artritis en psoriasis, systemische JIA (met algemene ziekte verschijnselen zoals koorts, lymfeklierzwelling, vergroting van organen), en 'andere artritis', wanneer een patiënt in geen enkele of meerdere categorieën kan worden ingedeeld.

De etiologie van JIA is onbekend. JIA wordt gezien als een auto-immuunziekte waarbij door een nog onbekende oorzaak bij kinderen met een genetische predispositie een ontregeling is ontstaan in het afweersysteem. Er bestaat geen specifieke test om de diagnose JIA te stellen. In Europa wordt de incidentie (het aantal nieuwe ziektegevallen) van JIA geschat op 1:10.000 kinderen, en de prevalentie (het voorkomen) op 1:1000 kinderen; in Nederland zijn tussen de 3000 en 4000 kinderen gediagnosticeerd met JIA en wordt de diagnose bij ongeveer 300 nieuwe patiënten per jaar gesteld. Voor JIA bestaat geen genezende behandeling; de meeste kinderen hebben continue of afwisselende perioden van gewrichtsontstekingen die voortduren tot in de volwassen leeftijd.

De gewrichtsontstekingen kunnen tot beschadiging van het gewricht leiden, en deze afwijkingen zijn veelal aan te tonen op röntgenfoto's. Zowel de gewrichtsontsteking als de gewrichtsbeschadiging leiden tot pijn en verminderde gewrichtsfunctie. De mate waarin schade van de gewrichten optreedt is afhankelijk van het soort JIA en de reactie op ingestelde therapie. De behandeling van JIA is gericht op het doen verdwijnen van de symptomen, het behouden van een goede gewrichtsfunctie en het leren omgaan met het wisselende ziektebeeld en bijkomende beperkingen.

De behandeling is multidisciplinair en omvat naast medicatie, fysiotherapeutische en ergotherapeutische begeleiding, met daarbij aandacht voor de emotionele ontwikkeling van het kind en begeleiding van het gezin.

In het hoofdstuk wordt een samenvatting gegeven van de ontwikkeling van de verschillende medicamenteuze behandelingsmogelijkheden voor JIA in de afgelopen decennia. Ook worden aspecten van het ziekteverloop, radiologische bevindingen, en ziekteuitkomst belicht. Tot slot bevat Hoofdstuk 1 een overzicht van farmacologische aspecten van SSZ en het gebruik van SSZ bij reumatologische aandoeningen.

Hoofdstuk 2 beschrijft de placebo-gecontroleerde SSZ-studie bij kinderen met JIA. Tot aan de jaren negentig bestond de medicatie bij JIA vooral uit NSAIDs (ontstekingsremmers, nonsteroidal antiinflammatory drugs) en werd pas bij lang bestaande ziekte overgegaan op prednison of andere DMARDs (antireumatica, disease-modifying antirheumatic drugs) die effectiviteit hadden aangetoond bij reumatoïde artritis (RA). Er bestonden weinig gecontroleerde DMARDs studies specifiek bij kinderen met JIA. Vanwege de goede werkzaamheid en veiligheid van SSZ bij RA besloot de Landelijke Werkgroep voor Kinderreumatologie tot het uitvoeren van de eerste gerandomiseerde, dubbelblinde, placebo-gecontroleerde SSZ studie om de werkzaamheid en veiligheid te analyseren bij kinderen met oligoarticulaire of polyarticulaire JIA. Omdat eerdere open studies hadden aangetoond dat kinderen met systemische JIA vaak bijwerkingen ondervonden van SSZ gebruik, werden zij voor inclusie uitgesloten.

De SSZ-studie duurde 24 weken, en 37 oligoarticulaire respectievelijk 32 polyarticulaire JIA patiënten werden geïncludeerd. Alle patiënten hadden minimaal één gewricht met actieve artritis (gewrichtszwelling of pijn met bewegingsbeperking) en een indicatie om te starten met een DMARD volgens de eigen behandelaar. Deelnemers werden behandeld met SSZ 50 mg/kg/dag (maximum 2000 mg/dag) in 2 doseringen of placebo.

Van de 69 deelnemers, volgde 75% het studie protocol volledig; 18% van de placebo groep stopte tussentijds, vooral vanwege gebrek aan effect, en 31% staakte behandeling in de SSZ groep, waarvan 29% door bijwerkingen. De studie resultaten (van alle deelnemers) toonden dat SSZ werkzamer was dan placebo in het onderdrukken van ziekteactiviteit: alle uitkomstscores waren beter voor de SSZ groep. Een lagere ziekte activiteit in de SSZ groep in vergelijk met de placebo groep was al aantoonbaar 12 weken na start van de behandeling, en de ziekteactiviteit bleef ook daarna lager in de SSZ groep. Aan het eind van de studie was de uitkomst significant beter in de SSZ groep voor wat betreft de gewrichtsscores, ziekte-activiteitscores door artsen, algemene scores van welbevinden door patiënten en ouders, ontstekingsparameters in het bloed en classificatie als 'verbeterd' volgens criteria voor verbetering in JIA studies.

Bijwerkingen kwamen significant meer voor in de SSZ groep, maar verdwenen bij iedereen volledig na het staken van SSZ. De bijwerkingen bestonden veelal uit maag-darmklachten, huiduitslag en laboratoriumafwijkingen. Eén patiënt ontwikkelde een overgevoeligheidsreactie in de derde week van therapie.

We concludeerden dat SSZ werkzaam en veilig is in de behandeling van kinderen met JIA, maar dat 30% van de kinderen last kan hebben van bijwerkingen.

In **Hoofdstuk 3** wordt ingegaan op een van de bijwerkingen van SSZ gebruik bij JIA: het ontstaan van te lage waarden van serum-immunoglobulinen (Ig) spiegels IgA, IgM, en IgG. We beschrijven het ziekteverloop van 6 kinderen met JIA bij wie deze bijwerking werd vastgesteld door het bepalen van serum-Ig spiegels tijdens SSZ gebruik. Geen van de kinderen had symptomen van deze bijwerking en geen van hen ontwikkelde een ernstige infectie. Bij alle kinderen normaliseerden de serum-Ig waarden na het staken van SSZ gebruik, echter bij 2 kinderen ontstonden gedurende de follow-up periode van 4-6 jaar opnieuw veranderingen in de immuniteit. Een kind ontwikkelde diabetes mellitus en een ander opnieuw een daling in serum-Ig spiegels. Ook bij volwassen RA patiënten werden incidenteel veranderingen van serum-Ig waarden gemeld bij het gebruik van SSZ, maar in de meeste studies werden de serum-Ig niet gemeten. De veranderingen van serum-Ig spiegels zijn waarschijnlijk het gevolg van de anti-inflammatoire en immunomodulatoire eigenschappen van SSZ. Het kan zijn dat kinderen met JIA meer gevoelig zijn voor het ontwikkelen van dit soort bijwerkingen aangezien zij ook meer andere immunoregulatoire afwijkingen tonen dan gezonde kinderen.

Op basis van deze studie en inzichten uit beschikbare literatuur adviseren wij tijdens SSZ gebruik serum-Ig spiegels te controleren.

In **Hoofdstuk 4** onderzoeken we of het bepalen van antilichamen tegen gecitrullineerde eiwitten (anti-CCP antilichamen) bij kinderen met JIA behulpzaam kan zijn bij het stellen van de diagnose JIA, dan wel bij het identificeren van kinderen met een progressief destructief ziekteverloop. Gecitrullineerde eiwitten zijn eiwitten waarvan het aminozuur arginine enzymatisch is veranderd in het aminozuur citrulline. Recent werd een test ontwikkeld om deze antilichamen aan te tonen (anti-CCP ELISA). In eerdere studies bij volwassenen met RA werd gevonden dat de aanwezigheid van anti-CCP zeer specifiek was voor RA en daarnaast van grote waarde voor het selecteren van patiënten met een agressief destructief ziekteverloop.

We analyseerden 100 serummonsters van 71 JIA patiënten, afkomstig uit alle subtypen JIA, op verschillende tijdstippen gedurende het ziekteverloop, op de aanwezigheid van anti-CCP. De mediane leeftijd was 10,5 jaar (spreiding 2-20) en ziekteduur 24 maanden (spreiding 3-245). Bevindingen werden gecorreleerd aan JIA subtypen, ziekte specifieke gegevens, medicatie en radiologische schade (aanwezigheid van gewrichtsspleetversmalling en / of erosies).

Anti-CCP was aantoonbaar bij 8 van 11 (73%) RF positieve JIA patiënten en in 2 (3%) van de andere JIA subtypen patiënten ($P < 0,0001$). Geen van de andere specifieke ziektekarakteristieken was verschillend tussen de anti-CCP positieve en anti-CCP negatieve patiënten. Uitslagen van vervolg serummonsters waren vergelijkbaar met de eerdere uitslagen. Alle RF positieve JIA patiënten toonden radiologische schade, maar de 2 anti-CCP positieve JIA patiënten zonder RF toonden geen radiologische schade. Dit betekende dat 80% van de anti-CCP positieve patiënten radiologische schade had, en er een significant hogere kans

was voor anti-CCP positieve patiënten in vergelijking met anti-CCP negatieve patiënten op het hebben van radiologische schade (odds ratio 12,7); maar bij correctie voor de correlatie tussen aanwezigheid van RF en anti-CCP was deze odds ratio niet meer significant.

We concludeerden dat anti-CCP antilichamen bij JIA patiënten kunnen worden aangetoond en vooral aanwezig zijn bij de RF positieve JIA subgroep. Een anti-CCP bepaling kan niet gebruikt worden ter bevestiging van de diagnose JIA in het algemeen. Er zijn aanvullende studies nodig om aan te tonen of de aanwezigheid van anti-CCP antilichamen bij JIA patiënten duiden op een ziekteverloop zoals bij RA en daarmee JIA patiënten selecteert met een progressief destructief ziekteverloop.

In de **Hoofdstukken 5 en 6** beschrijven we de ontwikkeling van een gestandaardiseerde radiologische scoringsmethode om röntgenfoto's te evalueren van kinderen met JIA die deelnemen aan klinische studies. Hoewel er voor volwassenen met RA verschillende gevalideerde scoringsmethodes voor bevindingen op röntgenfoto's bestaan kunnen deze bij kinderen met JIA niet worden gebruikt door de verschillen in uitingen van beide ziektebeelden (zoals effecten op de groei, verschil in verdeling van aangedane gewrichten, en het veelal later in het ziekteproces optreden van erosies bij JIA). In de eerste radiologische studie (**hoofdstuk 5**) beschrijven we de radiologische observaties bij kinderen met JIA op een gestandaardiseerde wijze, testen we de betrouwbaarheid en haalbaarheid van deze methode en correleren we de radiologische bevindingen met klinische symptomen.

Voor deze studie maakten we gebruik van de röntgenfoto's en klinische data van de deelnemers aan de placebo-gecontroleerde SSZ-studie welke beschreven zijn in hoofstuk 2. Alle foto's gemaakt bij studie inclusie (van klinisch aangedane gewrichten en contra-laterale gewrichten) werden gescoord op aanwezigheid of afwezigheid van een breed spectrum van radiologische uitingen bij JIA volgens de Dijkstra score: weke delen zwelling, osteopenie, gewrichtsspleetversmalling, groei veranderingen, subchondrale botcysten, erosies, en standsafwijkingen. Per patiënt werden alle 68 klinisch onderzochte gewrichten afgebeeld op maximaal 19 radiologische opnames van gewrichten (of gewrichtsgroepen).

Data van 67 van de 69 SSZ-studie deelnemers konden worden geanalyseerd. De gemiddelde leeftijd was 9,1 jaar (spreiding 2,5-17,6), de mediane ziekteduur was 24 maanden (spreiding 5-176), en het gemiddeld aantal gefotografeerde gewrichten per patiënt was 7 (spreiding 2-15).

De onderzoeksresultaten toonden dat knieën, handen en voeten het meest frequent radiologisch waren aangedaan. Radiologische afwijkingen in minimaal 1 gewricht werden bij 87% van de patiënten gezien. Weke delen zwelling kwam het meest frequent voor (bij 63% van de patiënten), gevolgd door groeiafwijkingen (bij 48%), gewrichtsspleetversmalling (bij 28%) en erosies (bij 15%). Van gewrichten met klinische symptomen toonde de helft ook afwijkingen op de röntgenfoto's; dit percentage was hoger (66%) in klinisch aangedane handen en voeten. Het was opvallend dat bij protocollair gefotografeerde (contralaterale) gewrichten zonder klinische symptomen relatief vaak radiologische afwijkingen werden beschreven; dit kwam vooral voor bij foto's van de handen en voeten (respectievelijk in 36% en 39%).

Aanvullende analyses toonden een goede correlatie tussen de ernst van de klinische bevindingen aan het gewricht en de aanwezigheid van radiologisch gescoorde afwijkingen. JIA patiënten met een positieve serum reumafactor (IgM-RF) en JIA patiënten positief voor het HLA-B27 antigeen, toonden significant vaker radiologische afwijkingen dan andere JIA patiënten. Over het algemeen was de radiologische score goed reproduceerbaar, hoewel de scores voor weke delen zwelling, osteopenie en groei afwijkingen het moeilijkst reproduceerbaar bleken. Gemiddeld duurde het scoren 10-20 minuten per patiënt.

We concludeerden dat onze radiologische scoringsmethode (later Dijkstra score genoemd) goed uitvoerbaar was, goed reproduceerbaar, goed correleerde met ernst van klinische gewrichtsafwijkingen, en tevens belangrijke nieuwe informatie toevoegde die niet aantoonbaar was bij klinisch onderzoek.

In **Hoofdstuk 6** evalueren we de gevoeligheid van de Dijkstra score voor het aantonen van verandering. Hiervoor gebruikten we zowel de studie inclusie als de 24-weken follow-up röntgen foto's van de SSZ-studie deelnemers. Deze bestonden uit 418 sets van klinisch aangedane en contralaterale gewrichten van 66 patiënten. Alle röntgenfoto's werden gescoord volgens de Dijkstra score.

Vervolgens definieerden we '*Dijkstra compositie scores*' voor een numerieke evaluatie van data: de *Dijkstra inflammatie (DI) score* (0-2): optelling van scores voor zwelling (0-1) en osteopenie (0-1); de *Dijkstra damage (DD) score* (0-3): optelling van scores voor gewrichtsspleetversmalling (0-1), botcysten (0-1) en erosies (0-1), en *Dijkstra groei (DG) score* (0-1): score voor aanwezigheid van groeiveranderingen. De DI, DD, en DG scores werden berekend bij studie inclusie en bij follow-up van alle gefotografeerde gewrichten en voor elke patiënt, en de scores op beide meetmomenten werden vergeleken. Een stijging van Dijkstra compositie scores impliceerde verslechtering, een daling verbetering. Een score voor standsverandering werd niet geëvalueerd vanwege onvoldoende data.

Gewrichtsschade werd vervolgens gecategoriseerd als '*progressief*' wanneer de DD of de DG score in een gewricht toenam; het ziekteverloop in gewrichten zonder toename van DD of DG als 'niet-progressief'. Alle scores werden geëvalueerd voor alle röntgenfoto's en per patiënt. Tevens werden de verschillen geanalyseerd tussen de beide behandelgroepen (SSZ en placebo).

De resultaten toonden dat de definities goed toepasbaar waren op de dataset van de SSZ-studie. Van de 66 patiënten toonde 12% geen afwijkingen op beide tijdstippen, behield 27% dezelfde radiologische afwijkingen en toonde 61% veranderingen in minstens één set röntgenfoto's. De DI en DD scores veranderden het frequentst in de knieën, terwijl de DD scores vooral veranderden in de handen en voeten. In 8% van de gewrichten werd het ziekteverloop geclassificeerd als progressief.

Ook was er verschil aantoonbaar tussen het ziekteverloop op de röntgenfoto's van SSZ en placebo patiënten: foto's van de SSZ patiënten toonden minder verslechtering in DD scores en het ziekteverloop was vaker geclassificeerd als non-progressief in de SSZ groep. Wanneer een '*progressor*' werd gedefinieerd als zijnde een patiënt met minimaal 1 röntgenfoto met

radiologische progressie, werden significant meer placebo patiënten geclassificeerd als 'progressor'.

Met deze studie was de initiële validatie van de Dijkstra score compleet. De Dijkstra compositie score en de progressor classificatie bleken in deze dataset gevoelig voor verandering en identificeerden verschil tussen 2 klinisch verschillende behandelsituaties. Om de Dijkstra score, Dijkstra compositie score en progressor classificatie verder te valideren is het nodig dat deze getest worden door andere onderzoekers in andere datasets.

Hoofdstuk 7. In de laatste studie van het proefschrift beschrijven wij de lange termijn uitkomst van de SSZ-studie deelnemers en analyseren of de verbeteringen die zich voordeden tijdens de SSZ-studie ook na langere tijd nog aantoonbaar waren. Voor deze follow-up studie werden in de periode 2001 tot 2003, 32 SSZ en 29 placebo patiënten (90% van alle deelnemers) mediaan 9 jaar na SSZ-studie deelname opnieuw onderzocht.

Na de trial werden de patiënten routinematig, zonder behandelprotocol, gecontroleerd en behandeld in gespecialiseerde reumatologische centra. Vrijwel alle patiënten continueerden of starten DMARDs (SSZ groep 91%, placebo groep 93%; SSZ als DMARD bij ongeveer 80% in beide groepen). De DMARD behandeling gedurende de follow-up periode van de SSZ groep was minder intensief dan in de placebo groep: zij gebruikten significant korter SSZ en er was een trend naar minder en korter methotrexaat gebruik, minder en korter ander DMARD gebruik, en ook het aantal patiënten dat DMARDs gebruikte bij follow-up was lager. Meer dan eenderde van de patiënten van beide groepen gaven aan gedurende de follow-up periode langere tijd niet therapietrouw te zijn geweest voor wat betreft het gebruik van DMARDs.

Bij follow-up had het merendeel (74%) van de patiënten actieve artritis en 30% actieve polyartritis. Ondanks de minder intensieve behandeling waren vrijwel alle uitkomstscores veel beter in de SSZ groep in vergelijking met de placebo groep. Verschillen waren significant voor wat betreft het aantal actieve gewrichten, de patiëntenscores voor algemeen welbevinden, het aantal patiënten dat een ziektevrije periode doormaakte zonder het gebruik van medicatie, de duur van de ziektevrije periodes, en het aantal patiënten zonder actieve artritis en geclassificeerd als 'verbeterd' volgens de criteria voor verbetering in JIA studies (ACR Pediatric 30 response).

In aanvullende analyses correleerde DMARD therapietrouw positief met een classificatie als 'verbeterd' volgens de criteria voor verbetering in JIA studies; gecorrigeerd voor deze correlatie, was de kans dat een patiënt uit de SSZ groep werd gekwalificeerd als 'verbeterd' ruim 4 maal zo groot als voor een placebo patiënt.

We concludeerden uit deze lange termijn uitkomststudie dat effectieve onderdrukking van ziekte-activiteit door SSZ vroeg in een actieve fase van JIA een verbetering geeft die ook op langere termijn zichtbaar is. Daarnaast werd het grote belang van therapietrouw bij DMARD gebruik aangetoond.

BESPREKING

Studies in dit proefschrift tonen aan dat SSZ effectiever is dan placebo in het onderdrukken van ziekte-activiteit en het verminderen van radiologische progressie bij kinderen met oligoarticulaire en polyarticulaire JIA. Ook beschrijven we dat de verbetering door SSZ gebruik tijdens de SSZ-trial lange tijd behouden blijft ondanks minder intensieve behandeling dan in de vroegere placebo groep. Deze bevindingen ondersteunen een behandelstrategie met vroege introductie van DMARDs bij actieve JIA. Tevens komt uit de vervolgstudie duidelijk naar voren dat goede DMARD therapietrouw leidt tot een betere uitkomst.

Sinds de start van de SSZ studie hebben nog 3 andere DMARDs in gecontroleerde studies effectiviteit aangetoond in het onderdrukken van ziekteactiviteit bij JIA: methotrexaat (MTX) (1992), etanercept (2000) en leflunomide (2005). Sinds de introductie van MTX in de behandeling van JIA zijn de effectiviteit en veiligheid van dit DMARD uitgebreid onderzocht. Vanwege de gunstige balans tussen werking en bijwerking, de eenmaal wekelijkse dosering, en verschillende praktische wijzen van toediening, is MTX inmiddels het meest gebruikte DMARD bij JIA behandeling. Etanercept is een goede therapeutische optie gebleken voor JIA patiënten die onvoldoende reageren op andere DMARDs; de hoge kosten en veiligheidsaspecten beperken het meer algemene gebruik van etanercept in JIA behandeling. De ervaring met leflunomide is nog zeer beperkt.

Behalve in de SSZ-trial is de effectiviteit van SSZ bij JIA behandeling ook in verschillende andere, veelal ongecontroleerde, studies aangetoond. In een aantal van deze studies werd het optreden van milde bijwerkingen ook gemeld; deze ontstonden veelal tijdens het begin van de behandeling, bestonden soms uit een overgevoeligheidsreactie, en verdwenen na het staken van SSZ. Het regelmatig controleren van bloed, vooral in de eerste maanden van therapie, wordt dan ook geadviseerd. Ouders en patiënten dienen goed te worden voorgelicht over de symptomen van bijwerkingen. In combinatie met de 2-maal daagse toediening, en de beperkte beschikbaarheid van verschillende toedieningsvormen, hebben deze praktische nadelen van SSZ behandeling het gebruik bij JIA beperkt.

In vergelijk met de andere DMARDs met aangetoonde effectiviteit bij JIA (MTX, etanercept, leflunomide) lijkt SSZ een 'matig actief' medicament wanneer de effectiviteit wordt uitgedrukt in gerapporteerde percentages van verbetering volgens de criteria voor verbetering bij JIA (ACR Pediatric 30 response). Een voorzichtige interpretatie van deze data is op zijn plaats omdat deelnemers in de studies verschilden voor wat betreft het JIA subtype, ziekteduur, ziekte-ernst, de evaluatie methoden en bijkomend medicatie gebruik. Het aantal effectiviteitstudies bij kinderen met JIA is gering in vergelijk met het aantal studies bij RA.

Het betrekken van een radiologische evaluatie om effectiviteit van DMARDs te beoordelen werd beperkt door het ontbreken van een gestandaardiseerde evaluatie methode voor studies bij JIA. Zoals beschreven in dit proefschrift, ontwikkelden wij de Dijkstra score, de Dijkstra compositie score en progressor classificatie, hetgeen een goed toepasbare methode

bleek om de röntgenfoto's behorende bij de SSZ-trial te beoordelen. De resultaten tonen dat SSZ effectiever is dan placebo in het vertragen van radiologische progressie, hetgeen overeenkomt met bevindingen in studies bij volwassenen met RA en SSZ. De Dijkstra score moet nog verder gevalideerd worden door andere onderzoekers en in andere data sets. Daarnaast willen we nog onderzoeken wat de bevindingen in de Dijkstra score op langere termijn betekenen; de röntgenfoto's van SSZ follow-up studie deelnemers kunnen hiervoor worden gebruikt.

Recent onderzoek bij volwassenen met RA heeft het grote belang van het betrekken van een radiologische evaluatie in effectiviteit studies van (combinatie) antireumatische therapie aangetoond. Uit verschillende studies blijkt dat er een discrepantie kan bestaan tussen klinische effectiviteit en radiologische ziekteprogressie. In toekomstige therapeutische studies bij JIA is het dan ook essentieel om een internationaal geaccepteerde, gevalideerde, gestandaardiseerde radiologische score te betrekken om de effectiviteit op radiologische progressie te beoordelen.

De uitkomst met de huidige behandelstrategieën bij JIA is teleurstellend. De in dit proefschrift gepresenteerde SSZ follow-up studie toont aan dat het merendeel van de patiënten een actieve artritis heeft bij het bereiken van de jong volwassen leeftijd. Het ziekteverloop kenmerkte zich door het afwisselen van periodes van meer en minder ziekte activiteit. Ook andere recente studies tonen aan dat de meeste patiënten het grootste deel van het ziekteverloop doorbrengen met actieve artritis.

Samenvattend betekent dit dat bij de meeste JIA patiënten de ziekteactiviteit onvoldoende is onderdrukt.

De resultaten uit de SSZ follow-up studie ondersteunen het concept van een 'window of opportunity' waarbij therapie in het begin van de ziekte effectiever is dan wanneer behandeling later in het ziekteverloop wordt geïntroduceerd. Dit leidt tot een strategie van snelle en volledige onderdrukking van ziekteactiviteit om beschadiging aan de gewrichten te voorkomen, dan wel te beperken, en een verdere ontwikkeling van immuundysregulatie te modificeren.

Hoewel de resultaten van de SSZ-studie het vroeg introduceren van SSZ bij oligo- en polyarticulair JIA ondersteunen, rechtvaardigen de goede korte termijn resultaten van hoge dosis MTX en etanercept behandeling de veronderstelling dat het eerder introduceren van deze therapieën op langere termijn tot nog betere resultaten kan leiden. Deze veronderstelling zal eerst dienen te worden onderzocht, zoals voor SSZ is gedaan. In afwachting van deze resultaten blijft SSZ een veilige behandelstrategie met een bewezen positief lange termijn effect.

Voor het toepassen van meer agressieve behandelstrategieën is het van belang patiënten met een te verwachten snel progressief ziekteverloop te kunnen identificeren. Uit de radiologische studie (hoofdstuk 5) blijkt dat IgM-RF positieve en HLA-B27 positieve JIA patiënten significant vaker radiologische afwijkingen tonen dan andere deelnemers. De consequentie van aanwezigheid van anti-CCP bij JIA dient nog verder te worden uitgezocht, maar het lijkt

terecht te veronderstellen dat de rol vergelijkbaar is met die zoals bij volwassenen met RA en is geassocieerd met een meer progressief destructief ziekteverloop. Het is te verwachten dat in de komende jaren andere serologische markers beschikbaar komen, dan wel vorderingen in genetisch onderzoek bijdragen aan de identificatie van patiënten die het meest kunnen winnen met een agressieve behandelstrategie.

Implicaties voor onderzoek

Toekomstig onderzoek zal zich richten op het verder verbeteren van de behandelstrategie bij JIA. In samenwerkingsverbanden, en met de ontwikkeling van behandelprotocollen gericht op een vroege en continue controle van ziekteactiviteit, kan worden geëvalueerd welke (combinatie van) conventionele DMARDs en nieuwere biologische middelen tot verbetering van ziekteuitkomst leiden zowel op korte als langere termijn. Het betrekken van een radiologische evaluatie is daarbij van essentieel belang, en nu ook mogelijk. Aandacht voor de zorg en ondersteuning van de patiënten zijn daarbij onontbeerlijk om de voorwaarden te scheppen voor een langdurige behandeling en goede therapietrouw.

Dankwoord

DANKWOORD

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Curriculum Vitae

CURRICULUM VITAE

Mary Antoinette Joan (Marion) van Rossum werd op 24 juni 1959 geboren te Eindhoven. Zij groeide op in Someren en behaalde in 1977 het VWO diploma aan het Peelland College te Deurne. Daarna studeerde zij geneeskunde aan de Vrije Universiteit te Amsterdam, en haalde het kandidaats examen in 1980 (cum laude), het doctoraalexamen in 1983, en het artsexamen in 1985 (cum laude).

In 1981 maakte ze tijdens een verblijf op een Nederlands ontwikkelingshulp project kennis met Afrikaanse gezondheidszorg in een 'Mother and Child Health Clinic' in Navrongo (Noord Ghana). Ze leerde Kiswahili aan het Taleninstituut in Amsterdam en vertrok in 1984 voor extracurriculaire stages tropengeneeskunde naar Kenia. Daar volgde ze een opleiding 'Lepra en Tuberculose management' in het Alupe Leprosy Hospital te Busia en werkte als 'post-graduate general physician' in het St. Joseph´s Hospital te Kilgoris en in het Mercy Mission Hospital te Eldama Ravine.

In 1985 startte ze aan het University College of San Diego in La Jolla (USA) de voorbereidingen op het Amerikaanse artsexamen (Foreign Medical Graduate Examination in the Medical Sciences, FMGEMS), dat ze in 1987 haalde.

De opleiding tot kinderarts begon ze in 1986 in het Academisch Ziekenhuis te Leiden en rondde ze in 1991 af (opleider prof.dr. L.J. Dooren†). Het niet-academische deel van haar opleiding deed ze in het Juliana Kinderziekenhuis te Den Haag (opleider dr. H.E. Zoethout). In het laatste jaar van haar opleiding tot kinderarts startte ze met de deelspecialisatie Immunologie en Reumatologie in het Wilhelmina Kinderziekenhuis te Utrecht, welke ze na een stage op de afdeling Reumatologie van het Universitair Medisch Centrum Utrecht in 1993 afrondde (opleiders prof.dr. W. Kuis, prof.dr. B.J.M Zegers, en prof.dr. J.W.J Bijlsma). Tijdens dit fellowship nam zij als lid van de werkgroep kinderreumatologie deel aan de sulfasalazine studie. Deze betrokkenheid leidde tot de studies beschreven in dit proefschrift onder leiding van prof.dr. B.A.C. Dijkmans (hoofd afdeling Reumatologie VU Medisch Centrum, Amsterdam).

Na haar fellowship werd zij in 1993 aangesteld als staflid op de afdeling Pediatrische Immunologie, Hematologie, Oncologie, en Beenmergtransplantatie in het Leids Universitair Medisch Centrum (hoofd prof.dr. J.M. Vossen en prof.dr. R.M. Egeler) te Leiden.

Vanaf 2003 is zij werkzaam als kinderarts met als aandachtsgebied reumatologie/auto-immuunziekten op de afdeling Klinische Immunologie, Hematologie en Infectieziekten (hoofd prof.dr. T.W. Kuijpers) van het Emma Kinderziekenhuis AMC (hoofd prof.dr. H.S.A. Heymans) en op de afdeling Reumatologie van het Jan van Breemen Instituut (hoofd dr. D. van Schaardenburg) te Amsterdam.

Marion is getrouwd met Ger Poppelaars en samen hebben zij een dochter Pomme (1997).

Publications

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