EXTENDED REPORT

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

Marion A J van Rossum, Renée M van Soesbergen, Maarten Boers, Aeilko H Zwinderman, Theo J W Fiselier, Marcel J A M Franssen, Rebecca ten Cate, Lisette W A van Suijlekom-Smit, Nico M Wulffraat, Wilma H J van Luijk, Johanna C M Oostveen, Wietse Kuis, Ben A C Dijkmans, on behalf of the Dutch Juvenile Idiopathic Arthritis Study group

Ann Rheum Dis 2007;**66**:1518–1524. doi: 10.1136/ard.2006.064717

See end of article for authors' affiliations

Correspondence to: Marion A J van Rossum, MD, PhD, Paediatric Rheumatologist, Emma Children's Hospital AMC, Paediatric Rheumatology, G8-205, PO Box 22660, 1100 DD Amsterdam, The Netherlands; m.a.vanrossum@amc.uva.nl

Accepted 14 April 2007
Published Online First 9 May 2007

Objectives: A previous 24-week randomised trial demonstrated that sulfasalazine (SSZ) treatment was superior to placebo (PLAC) in suppressing disease activity in patients with oligo- 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 prospectively examined clinically and by chart review, median 9 years (range 7 to 10) after trial inclusion. In the follow-up assessment, variables of the American College of Rheumatology Pediatric 30 (ACR Pedi 30) criteria were collected. The assessor was blinded to trial treatment allocation.

Results: After the trial, patients had been routinely followed in rheumatology referral centres, and treated at the discretion of the attending physician. Almost all patients continued or started disease-modifying antirheumatic drugs (DMARDs) (SSZ 91%, PLAC 93%; SSZ treatment in about 80%). DMARD treatment appeared 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 less use of methotrexate and other DMARDs. More than one-third of the patients reported long periods of non-compliance with DMARD treatment in both groups.

At follow-up, 74% of the patients had active joints, and 30% showed active polyarthritis. Almost all outcome scores were better for SSZ compared with PLAC patients. Differences (often exceeding 50%) were significant for the number of active joints, patients' overall well-being, number of patients with episodes of clinical remission off medication (CROM) and duration of these episodes, patients in CROM and ACR Pedi 30 response at follow-up. Additional exploratory analyses performed to detect potential confounders related to patient characteristics or follow-up treatment showed that DMARD treatment compliance was positively correlated with an ACR Pedi 30 response (odds ratio 3.8, 95% confidence interval (CI) 1.1 to 13.4; p = 0.03). Adjusted for compliance, an 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 to 14.3; p = 0.02).

Conclusions: This follow-up 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.

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 disease-modifying antirheumatic drug (DMARD) treatment in JIA changed in the early 1990s.[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 favourable, but the long-term effects are unknown.[12]

In the period 1992–1994, we conducted a 24-week randomised 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 paediatric rheumatology referral centres 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.

Abbreviations: CROM, clinical remission off medication; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; JIA, juvenile idiopathic arthritis; LOM, limitation in range of motion; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory; PGAS, physician's global assessment of disease activity score; PLAC, placebo; SSZ, sulfasalazine

PATIENTS AND METHODS

Design

The study is a cohort follow-up of a randomised trial. Patients and their medical records were prospectively examined once by the principal investigator in a series of site visits between 2001 and 2003.

Patients

All participants of the multicentre, double-blind, randomised, 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 to 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 obtained according to the legal requirements. Eligible patients who declined participation in the follow-up study were asked permission to retrieve the most recent data on disease status and treatment from their medical records.

Procedures

The database of the SSZ trial was used for data on onset of arthritis; randomisation to PLAC or SSZ treatment; joint scores, general assessments, laboratory data and adverse events during the trial. Patients' medical records were retrospectively reviewed for the following information: clinical data (presence of arthritis; occurrence of uveitis, and medical problems which came to the attention of the treating physician); laboratory data (presence of rheumatoid factor); treatment data (NSAIDs, disease-modifying antirheumatic drug (DMARDs), systemic corticosteroids, immunosuppressive drugs, antitumour 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.

Outcome assessments

Participants were asked to visit one of the centres for physical examination, completion of questionnaires and laboratory assessment. An 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 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, the physician's global assessment of disease activity 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, 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 analysed together.[8 22 23] The CHAQ and HAQ scores (C-HAQ scores) were summarised in the disability index ranging from 0 to 3, with higher scores meaning a higher disability.[23] For facilitation of comparison with other outcome studies, the C-HAQ scores were divided into 4 categories of disability: 0 = none; 0–0.5 as mild; 0.6–1.5 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 highly sensitive latex-enhanced assay supplied by Roche Diagnostics (Almere, The Netherlands) on a Hitachi 911 analyser (Roche Diagnostics), according to the manufacturer's instructions. IgM-RF was measured using an inhouse enzyme-linked immunosorbent assay and an ES 300 analyser (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) PGAS and (4) ESR. Patients were classified as improved when they showed at least 30% improvement in 3 of the 4 aforementioned variables, and not one of the variables could be worsened by more than 30%.

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 analysed 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, 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/McNemar test for paired related samples. Overall differences in outcome between the JIA subgroups were tested using non-parametric analysis: Fisher's exact, Mann–Whitney, Kruskal–Wallis or χ^2 test where appropriate. At follow-up, individual outcome was described using the physicians' disease activity score (dichotomised with group median PGAS level as a 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 (χ^2 and t test where appropriate) were: oligo- or polyarticular onset type of JIA, gender, age at onset, rheumatoid factor positive JIA subtype classification, JIA duration before introduction of DMARD therapy, number of used DMARDs in the follow-up period, duration of SSZ treatment, duration of methotrexate (MTX) treatment, reported DMARD therapy compliance, JIA duration at follow-up, and randomisation to SSZ or PLAC in the trial; followed by a multivariate model to determine the independent factors related with outcome. For all analyses, p values less than or equal to 0.05 were considered statistically significant.

RESULTS

In the original SSZ trial, 69 oligoarticular- and polyarticular onset JIA patients were enrolled.[13] One patient was evaluated as ineligible and excluded from the 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 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%).

In the original trial, 34 patients were randomised 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 5 patients that refused further follow-up examinations included: 1 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 to 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 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.

The 61 participants in the follow-up study were examined at a median age of 18 years (range 10 to 25) and median disease duration of 10.7 years (range 8 to 23). The median interval between SSZ trial inclusion and the follow-up visit was 9 years (interquartile range (IQR) 8 to 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 with polyarticular JIA onset patients ($p = 0.002$).

Changes in classification of JIA subtype between trial inclusion and follow-up assessment occurred in 11 patients and were comparable in both treatment groups: 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.

General physical outcome

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 body weight was within the normal range.[26] The mean age for menarche was 13 years (range 10 to 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.

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 with 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 to 2). None to mild disability was reported by 74% of the patients, moderate disability by 20% and severe disability by 6% of the patients.

Follow-up of treatment per trial group

Thirty-two (52%) of the 61 study participants available for follow-up had been randomised to SSZ and 29 (48%) to PLAC. Treatment before SSZ trial start 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 to 4.9). In due course, 16 (50%) SSZ patients switched to another DMARD treatment, including MTX in 15 (47%). The median duration of MTX treatment of those SSZ patients was 3.0 (IQR 1.5 to 5.0) years. The 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 to 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

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

Variable	Placebo group n = 29	Sulfasalazine group n = 32	p value
Females	20 (69%)	21 (66%)	0.8
Age, median years (range)	19 (10 to 23)	16 (10 to 25)	0.1
Disease duration, median years (range)	10 (8 to 20)	11 (8 to 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 years (range)	8 (2 to 14)	3 (1 to 15)	0.02§
Age at start SSZ trial inclusion, median, years (range)	11 (3 to 15)	8 (3 to 17)	0.1
Disease duration at start DMARD therapy: median, years (range)†	1.8 (0.5 to 12)	2.1 (0.4 to 13.2)	0.6
Oligoarticular onset JCA patients	2.5 (0.5 to 12.3)‡	3.0 (0.5 to 13.2)‡	0.8
Polyarticular onset JCA patients	1.1 (0.7 to 5.5)	1.5 (0.4 to 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; †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 with polyarticular onset JCA patients (p = 0.002); §SSZ allocated patients were significantly younger at disease onset but were of a 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)

group: 5.2 years (IQR 2.1 to 8.0; p = 0.02). A similar (non-significant) 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 to 5.8) years. The median number of DMARDs used in the follow-up period by PLAC patients was 2 (range 0 to 5).

Prednisone was rarely prescribed. During follow-up, 1 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, outcome scores were better in the SSZ group compared with 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 response, patients with episodes of clinical remission off medication (CROM), duration of CROM episodes, and patients in CROM at the follow-up assessment. Results were unchanged when 10 rheumatoid factor-positive JIA subtype patients were excluded from analyses (results not shown).

The ACR Pedi 30 response 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 with 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 with 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

Table 2 Long-term outcome after median 9 years in comparison with trial data of 61 juvenile idiopathic arthritis patients who participated in a randomised placebo-controlled sulfasalazine trial[13]*

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 to 71)	5 (3 to 11)	2 (1 to 7)	2 (0 to 6)	NS
Limited joints (range 0 to 67)†	4 (1 to 7)	2 (1 to 5)	5 (2 to 12)	<0.001
Physician's score of disease activity (range 0 to 5)‡	3 (3 to 4)	2 (1 to 3)	2 (1 to 3)	NS
Erythrocyte sedimentation rate mm/h	27 (11 to 43)	11 (6 to 22)	8 (5 to 22)	NS
C-reactive protein mg/l	6 (1 to 29)	2 (1 to 11)	2 (1 to 6)	NS
No. (%) of patients with				
No active joints	0	14 (23%)	16 (26%)	NS
No limited joints	6 (10%)	9 (15%)	6 (10%)	NS
>4 active joints	36 (59%)	20 (33%)	18 (30%)	NS
>4 limited joints	26 (43%)	18 (30%)	33 (54%)	<0.001

*Values are given in median and interquartile range (IQR 25 to 75%) or number and percentage as indicated; †limited joints = joints with limitation in range of motion;[17] ‡PGAS: 0 = none; 1+ = very low; 2+ = low; 3+ = moderate; 4+ = active; 5+ = very active.

Table 3 DMARD use in the follow-up period from SSZ trial inclusion to review for follow-up of 61 juvenile idiopathic arthritis patients who participated in a placebo-controlled sulfasalazine trial[13]*

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 to 5)	1.5 (1 to 5)	NS
No. (%) of patients with SSZ use	24 (83)	32 (100)	0.02
Duration of SSZ use in years, median (IQR)	5.2 (2.1 to 8.0)	2.5 (0.5 to 4.9)	0.02
No. (%) of patients with MTX use	16 (55)	15 (47)	NS
Duration of MTX use in years, median (IQR)	4.0 (3.0 to 5.8)	3.0 (1.5 to 5.0)	NS
No. (%) of patients with prednisone use	3 (10)	2 (6)	NS
Duration of prednisone use in years, median (IQR)	2.0 (2.0 to 6.0)	0.9 (0.3 to 1.5)	NS
No. (%) of patients with intramuscular gold use	3 (10)	5 (16)	NS
Duration of intramuscular gold use in years, median (IQR)	4.0 (1.5 to 7.0)	1.5 (0.5 to 2.8)	NS
No. (%) of patients with hydroxychloroquine use	0	3 (9)	–
Duration of hydroxychloroquine use in years, median (IQR)	0	6.2 (0.1 to 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)	NS
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	–
Antitumor necrosis factor	0	1	–

*SSZ, sulfasalazine; HCQ, hydroxychloroquine; †other DMARDs included: in 1 PLAC patient: 9 months' treatment with ciclosporin and an autologous bone marrow transplantation,[27] respectively in 1 SSZ patient: 6 months of leflunomide treatment followed by recent introduction of anti-TNF-treatment.

strong 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 clinical remission off medication ($p = 0.007$) and 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 exploratory analyses to detect potential confounders in the relationship between group allocation in the original trial and outcome. For these analyses, good outcome was defined as PGAS $\leqslant 2$ or the presence of ACR Pedi 30 response at follow-up. In univariate analysis, a PGAS good outcome was associated with allocation to the SSZ group (OR 3.5 (95% CI 1.1 to 11.1), $p = 0.03$), male sex (OR 6.4 (1.3 to 31.0), $p = 0.01$) and compliance (OR 4.3 (1.4 to 13.5), $p = 0.01$). In multivariate analysis, male sex (OR 6.0 (1.2 to 31.0), $p = 0.03$) and compliance (OR 4.1 (1.2 to 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 (95% CI 0.6 to 12.5, $p = 0.06$) than the odds for PLAC.

In a univariate analysis, the ACR Pedi 30 response correlated positively with allocation to SSZ (OR 4.2 (1.3 to 13.9), $p = 0.02$) and compliance with DMARD therapy (OR 3.8 (1.1 to 13.4),

Table 4 Comparison of outcome variables of PLAC and SSZ patients who participated in a placebo-controlled sulfasalazine trial[13] and long-term follow-up study*

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

*Values are median and interquartile range (IQR), unless otherwise indicated. PLAC, placebo; SSZ, sulfasalazine; NA, not applicable; C-HAQ, CHAQ and HAQ results combined. 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); †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 ($p<0.001$); ‡improvement according to the ACR Paediatric 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.

p = 0.03). Duration of MTX treatment (OR 0.7 (0.5 to 0.97), p = 0.02) and number of DMARDs used during the follow-up period (OR 0.4 (0.2 to 0.9), p = 0.03) correlated negatively with ACR Pedi 30 response. In multivariate analysis, only compliance remained a significant factor. Adjusted for compliance, the odds for ACR Pedi good outcome were 4.2 times higher (1.3 to 14.3, p = 0.02) in the SSZ group than the odds for PLAC. Adjustment in addition for duration of MTX treatment and number of DMARDs used during the follow up period changed the odds ratio for the presence of the ACR Pedi 30 response in the SSZ group to 4.7 (1.2 to 18.3, p = 0.03).

The study group was too small to reliably analyse 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 better health than patients in the PLAC group: numerical differences, often exceeding 50%, 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 DMARD in active JIA. Patients' compliance with prescribed DMARD treatment appeared to be another important factor related to the 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 but not yet in JIA.[30–34] 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 1990s, treatment of the study participants can be qualified as intensive compared with 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 that unrelenting attention to this issue is needed in daily practice.

This study has limitations. Treatment initiation would not be called early by current standards. In addition, 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. The observation that in both treatment groups, the delay of DMARD introduction was similar in oligoarticular respectively polyarticular onset JIA precluded this form of treatment bias. We cannot completely rule out that despite stratification per JIA onset subtype and randomisation 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 organise these type of studies.

In summary, this is the first follow-up study to show that effective suppression of disease activity by SSZ treatment early in an active phase of disease in oligo- 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.

ACKNOWLEDGEMENTS

We thank the following rheumatologists for their participation: Nanno WAA Swen, Jacques JAPM Ewals, André AJ Peeters, Miek M van Leeuwen, Judith JM van Emmerik, Erna PJ Barendrecht, Barbara van Schaeybroeck, and Toon AAA Westgeest; biochemist Rob RJ van der Stadt and technician Margret MHMT de Koning for all laboratory assessments; Nora Schram for writing the computer program and setting up of the database; and research nurse Elleke H de Wit-Taen, for assistance in patient recruitment, data collection, data management and coordination of the study. The study was financially supported by the Dutch Arthritis Association.

Authors' affiliations

Marion A J van Rossum, Emma Children's Hospital AMC, Amsterdam, The Netherlands, and Department of Rheumatology, Jan van Breemen Instituut, Amsterdam, The Netherlands
Renée M van Soesbergen, Department of Rheumatology, Jan van Breemen Instituut, Amsterdam, The Netherlands
Maarten Boers, Department of Clinical Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands
Aeilko H Zwinderman, Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam, The Netherlands
Theo J W Fiselier, Department of Paediatrics, Radboud University Medical Centre, Nijmegen, The Netherlands
Marcel J A M Franssen, Department of Rheumatology, St Maartenskliniek, Nijmegen, The Netherlands
Rebecca ten Cate, Department of Paediatrics, Leiden University Medical Centre, Leiden, The Netherlands and Department of Paediatrics, Erasmus MC/Sophia Children's Hospital, Rotterdam, The Netherlands
Lisette W A van Suijlekom-Smit, Department of Paediatrics, Erasmus MC/Sophia Children's Hospital, Rotterdam, The Netherlands
Nico M Wulffraat, Wietse Kuis, Department of Paediatrics, University Medical Centre Utrecht, Utrecht, The Netherlands
Wilma H J van Luijk, Department of Paediatrics, University Medical Centre Groningen, Groningen, The Netherlands
Johanna C M Oostveen, Department of Rheumatology, Twenteborg Ziekenhuis, Almelo, The Netherlands
Ben A C Dijkmans, Department of Rheumatology, VU University Medical

Centre, Amsterdam, The Netherlands, and Department of Rheumatology, Jan van Breemen Instituut, Amsterdam, The Netherlands

Competing interests: None declared.

REFERENCES

1 **Oen K**, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. *J Rheumatol* 2002;**29**:1989–99.
2 **Oen K**, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Reed M, Schroeder ML, Cheang M. Early predictors of outcome in patients with Juvenile Rheumatoid Arthritis: subset-specific correlations. *J Rheumatol* 2003;**30**:585–93.
3 **Flatö B**, Lien G, Smerdel A, Vinje O, Dale K, Johnston V, *et al*. Prognostic factors in juvenile arthritis: a case-control study revealing early predictors and outcome after 14.9 years. *J Rheumatol* 2003;**30**:386–93.
4 **Bowyer SL**, Roettcher PA, Higgins GC, Adams B, Myers LK, Wallace C, *et al*. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. *J Rheumatol* 2003;**30**:394–400.
5 **Ravelli A**, Martini A. Early predictors of outcome in juvenile idiopathic arthritis. *Clin Exp Rheumatol,* 2003;**21**(suppl 31), S89–93.
6 **Fantini F**, Gerloni V, Maurizio G, Cimaz R, Cristina A, Lupi E. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. *J Rheumatol* 2003;**30**:579–84.
7 **Andersson Gäre B**, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. I. Onset and disease process. *J Rheumatol* 1995;**22**:295–307.
8 **Ruperto N**, Levinson JE, Ravelli A, Shear ES, Link Tague B, Murray K, Martini A, Giannini EH. Longterm health outcomes and quality of life in American and Italian Inception cohorts of patients with juvenile rheumatoid arthritis. I Outcome status. *J Rheumatol* 1997;**24**:945–51.
9 **Zak M**, Pederson FK. Juvenile chronic arthritis into adulthood: a long-term follow-up study. *Rheumatology* 2000;**39**:198–204.
10 **Packham JC**, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology* 2002;**41**:1428–35.
11 **Wallace CA**, Levinson JE. Juvenile rheumatoid arthritis: outcome and treatment in the 1990s. *Rheum Clin North Am* 1991;**17**:891–905.
12 **Murray KJ**. Advanced therapy for juvenile arthritis. *Best Pract Res Clin Rheumatol* 2002;**16**:361–78.
13 **Van Rossum MAJ**, Fiselier TJW, Franssen MJAM, Zwinderman AH, ten Cate R, van Suijlekom-Smit LWA, *et al*. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. *Arthritis Rheum* 1998;**41**:808–16.
14 **Wood PHN**. Nomenclature and classification of arthritis in children. In: Munthe E, eds. *The care of rheumatic children*. Basel: EULAR, 1978:47–50.
15 **Petty RE**, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He Xiaohu. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton 2001. *J Rheumatol* 2004;**31**:390–2.
16 **Duffy CM**, Colbert RA, Laxer RM, Schanberg LE, Bowyer SL. Nomenclature and classification in chronic childhood arthritis. *Arthritis Rheum* 2005;**52**:382–5.
17 **Brewer EJ**, Giannini EH. Standard methodology for segment I, II, and III Pediatric Rheumatology Collaborative Study Group studies. I. Design. *J Rheumatol* 1982;**9**:109–13.
18 **Ruperto N**, Giannini EH. Redundancy of conventional articular response variables used in juvenile chronic arthritis trials. *Ann Rheum Dis* 1996;**55**:73–5.
19 **Ravelli A**, Viola S, Ruperto N, Corsi B, Ballardini G, Martini A. Correlation between conventional disease activity measures in juvenile chronic arthritis. *Ann Rheum Dis* 1997;**56**:197–200.
20 **Wulffraat N**, Van der Net JJ, Ruperto N, Kamphuis S, Prakken BJ, Ten Cate, et al. The Dutch version of the childhood health assessment questionnaire (CHAQ) and the child health questionnaire (CHQ). *Clin Exp Rheumatol,* 2001;**19**(suppl 23), S111–5.
21 **Siegert C**, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. *Clin Rheumatol* 1984;**3**:305–9.
22 **Singh G**, Athreya B, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum* 1994;**37**:1761–91.
23 **Ruperto N**, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L, *et al*. Cross-cultural adaptation and psychometric evaluation of the childhood health assessment questionnaire (CHAQ) and the child health questionnaire (CHQ) in 32 countries. Review of the general methodology. *Clin Exp Rheumatol* 2001;**19**(suppl 23):S1–9.
24 **Wallace CA**, Ruperto N, Giannini EH. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;**31**:2290–4.
25 **Giannini EH**, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;**40**:1202–9.
26 **Fredriks AM**, Van Buuren S, Burgmeijer RJF, Meulmeester JF, Beuker RJ, Brugman E, *et al*. Continuing positive secular growth change in the Netherlands 1955–1997. *Pediatr Res* 2000;**47**:316–23.
27 **De Kleer IM**, Brinkman DMC, Ferster A, Abinun M, Quartier P, van der Net J, *et al*. Autologous stem cell transplantation for refractory juvenile idiopathic arthritis: analysis of clinical effects, mortality, and transplant related morbidity. *Ann Rheum Dis* 2004;**63**:1318–26.
28 **Van Rossum MA**, Fiselier TJ, Franssen MJ, ten Cate R, Van Suijlekom-Smit LW, Wulffraat NM, *et al*. Effects of sulfasalazine treatment on serum immunoglobulin levels in children with juvenile chronic arthritis. *Scand J Rheumatol* 2001;**30**:25–30.
29 **Van Rossum MA**, Boers M, Zwinderman AH, Van Soesbergen RM, Wieringa H, Fiselier TJ, *et al*. Development of a standardized method of assessment of radiographs and radiographic change in juvenile idiopathic arthritis. *Arthritis Rheum* 2005;**52**:2865–72.
30 **Egsmose C**, Lund B, Borg G, Petterson H, Berg E, Brodin U, Trang L. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. *J Rheumatol* 1995;**22**:2208–13.
31 **Tsakonas E**, Fitzgerald AA, Fitzcharles M, Cividino A, Thorne JC, M'Seffar A, *et al*. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on hydroxychloroquine in early rheumatoid arthritis (HERA) study. *J Rheumatol* 2000;**27**:623–9.
32 **Landewé RBM**, Boers M, Verhoeven AC, Westhovens R, van de Laar MAFJ, Markusse HM, *et al*. COBRA combination therapy in patients with early rheumatoid arthditis. Long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002;**46**:347–56.
33 **O'Dell**. Treating rheumatoid arthritis early: a window of opportunity? *Arthritis Rheum* 2002;**46**:283–5.
34 **Boers M**. Understanding the window of opportunity concept in early rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:1771–4.
35 **Silverman E**, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, *et al*. Leflunamide or methotrexate for juvenile idiopathic arthritis. *N Engl J Med* 2005;**352**:1655–66.
36 **Hashkes PJ**, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA* 2005;**294**:1671–84.
37 **Michaud PA**, Suris JC, Viner R. The adolescent with a chronic condition. Part II: healthcare provision. *Arch Dis Child* 2004;**89**:943–9.