Long-term outcome of anti-tumour necrosis factor alpha blockade in the treatment of juvenile spondyloarthritis

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Abstract

Objective

A significant proportion of patients with juvenile spondyloarthritis (JSpA) are refractory to treatment with established medications. The objective of this study was to assess long-term efficacy of treatment with anti-TNF agents in patients with JSpA.

Methods

An observational study of 16 patients with JSpA from 3 centres treated with infliximab (n=10) and etanercept (n=6) was performed, with a median follow-up period of 7.2 years. Prospective data was collected according to a standardised protocol. Outcomes examined were TEC, TAJC, markers of inflammation (ESR, CRP), functional assessments (C-HAQ, BASDAI, BASFI), and ongoing requirement for anti-TNF treatment.

Results

13/16 patients (83%) had achieved clinical remission 6 months into the treatment. Improvement was sustained over time, with a median TAJC and TEC of 0 at any time point after 6 weeks. 6/16 patients (38%) showed a flare of arthritis after a median of 3.5 years. Two patients with hip disease prior to treatment required an arthroplasty 3 and 8 years post anti-TNF initiation. Patients showed progression of sacroiliitis with median modified New York score of 1 (range 0–3) at time of diagnosis and 3 (range 0–4) at last follow-up (p=0.002). Median BASDAI at last follow-up was 1.6, median BASFI 3.1. Two patients developed transient reactions (one generalised, one local); no patient developed other adverse effects during the study.

Conclusion

Anti-TNF treatment in JSpA refractory to standard treatment results in good long-term disease control except for pre-existing hip disease. However, radiographic evidence suggests inferior efficacy for control of sacroiliac joint disease.

Key words

juvenile idiopathic arthritis, juvenile spondyloarthritis, enthesitis-related arthritis, anti-TNF treatment, sacroiliitis

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Introduction

Juvenile Spondyloarthritis (JSpA) represents a group of chronic inflammatory diseases affecting the axial and peripheral skeleton in children below the age of 16. JSpA includes enthesitis-related arthritis (ERA) in the current International League of Associations for Rheumatology (ILAR) classification of Juvenile Idiopathic Arthritis (JIA) (1). Other disease entities such as psoriatic arthritis and arthritis associated with inflammatory bowel disease also are part of the spectrum, as described by the Classification Criteria of the European Spondyloarthropathy Study Group (ESSG) (2). Rarely, JSpA has been reported to coexist with other JIA subtypes (3). JSpA is commonly characterised by peripheral arthritis and enthesitis, particularly in the lower limbs, and may also evolve to have axial involvement of the spine and sacroiliac joints. The HLA-B27 histocompatibility antigen is frequently found in JSpA patients. JSpA can lead to significant long term morbidity especially when the hips or spine are affected, and patients with JSpA show a worse functional outcome than patients with the adult-onset type (4). There are varying reports on the functional outcomes of patients with JSpA compared with adult-onset SpA (5).

Previously, JSpA treatment consisted of non-steroidal anti-inflammatory drugs (NSAIDs) and local and systemic corticosteroids, which provide symptomatic relief, but have little effect on long term damage. Treatment with second-line agents, disease-modifying drugs (DMARDs) used in other forms of JIA, have yielded only modest benefits (6). Antibodies against tumour necrosis factor α (TNF-α antagonists) have been shown to have good efficacy in adult-onset spondyloarthritis (7, 8). TNF-α antagonists have been established as safe and are well tolerated in paediatric patients with other forms of JIA as well as inflammatory bowel disease (IBD). A small study on 10 patients with JSpA (all of whom met the criteria for ERA) treated with either etanercept or infliximab was performed previously. After one year, all patients showed significant improvement in number of active joints and tender entheses, as well as markers of inflammation and functional assessments (9). However, no long term safety and efficacy data exists for the use of TNF-α antagonists in the paediatric population with ERA. Despite this, the recommendations of the American College of Rheumatology list TNF antagonists as prominent treatment options for all forms of JIA, especially in active sacroiliac arthritis (10).

The aim of this open-label study was to describe the long-term efficacy and safety of patients with JSpA refractory to NSAIDs and DMARDs treated with anti-TNF-α blockade.

Patients and methods

Study design

A longitudinal observational study of patients selected from the databases of The Hospital for Sick Children, Toronto, Canada, the Toronto Western Hospital, Toronto, Canada and the Hospital General de Mexico, Mexico City, Mexico, was performed. All three hospitals are tertiary care centres in their communities who provide specialised paediatric and/or adult rheumatology service. Inclusion criteria were: (I) a diagnosis of JSpA as defined by the European Spondyloarthropathy Study Group (ESSG) (2); (II) fulfillment of the diagnostic criteria for the subgroup of enthesitis-related arthritis (ERA) or juvenile psoriatic arthritis (PsA), as defined by the International League of Associations for Rheumatology criteria for JIA (1), or the concurrent diagnosis of IBD and arthritis; (III) persistent arthritis and/or enthesitis despite treatment with appropriate doses of NSAIDs and other drugs (including corticosteroids, methotrexate and sulfasalazine). These criteria were chosen to reflect the cohort of the previous study (9). Exclusion criteria were: (I) age >16 years at diagnosis, (II) previous treatment with anti-TNF medications; (III) contraindications to treatment with anti-TNF medications; (IV) follow-up on anti-TNF treatment of less than two years. Patients initially received either infliximab (infusions of 5mg/kg at weeks 0, 2, 6 and every 8 weeks subsequently) or etanercept (0.4 mg/kg subcutaneously twice weekly up to a maximum dose of 25 mg per

injection). Choice of anti-TNF-α therapy was based on drug availability and coverage from each patient's medical insurance plan. Ten patients had already been reported in a previous study with shorter follow-up (9). The study was approved by the Research Ethics Board of The Hospital for Sick Children (REB File No. 1000005740).

Data collection

The data were compiled from a retrospective chart review of all study patients, using standardised data collection forms, at baseline, 6 weeks, 6 months, and in yearly intervals thereafter. Information extracted included demographic data, medication history and current medication, total active joint count (TAJC) and tender entheseal count (TEC), markers of inflammation including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), sacroiliac joint diagnostic imaging data, joint replacements, disease activity assessment using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and functional assessment using the Bath Ankylosing Spondylitis Functional Index (BASFI) (11, 12) and the Childhood Health Assessment Questionnaire (C-HAQ) (13) or Health Assessment Questionnaire (HAQ), where appropriate. Adverse events were continually recorded in a dedicated database (The Hospital for Sick Children and Toronto Western Hospital) or retrospectively extracted by chart review (Hospital General de Mexico).

Definitions

Active joint: 'Active joint' was defined as the presence of a joint effusion, or at least 2 of the following signs/symptoms: warmth, pain/tenderness, or limited range of movement, on physical examination.

Enthesitis: 'Enthesitis' was defined by the patients' response, elicited as pain, wincing, or withdrawal upon firm palpation over the entheseal insertions.

Clinical remission: 'clinical remission' was defined as achieving both a TAJC and TEC of 0 at the time of assessment.

Flare: 'Flare' was defined as any increase in the TAJC in a patient after achieving clinical remission (irrespective of TEC).

Table I. Demographic and clinical characteristics of the study patients (n=16).

Demographics and clinical features	
Female:Male	2:14
Diagnosis	
Juvenile ankylosing spondylitis	4
Enthesitis-related arthritis	8
Psoriatic arthritis	1
SEA syndrome	1
Undifferentiated spondyloarthritis	2
IBD-associated arthritis	1
Median age at diagnosis (range)	11.1 years (6.2 - 15.7)
Median age at start of anti-TNF treatment (range)	14.9 years (11.4 – 19.8)
Median follow-up (range)	7.2 years (4.5 – 12.1)
HLA-B27 positive (%)	15/16 (93%)
Anti-nuclear antibodies positive (%)	0/15 (0%)
Rheumatoid factor positive (%)	0/15 (0%)
Previous treatment	
Non-steroidal anti-inflammatory drugs	16/16 (100%)
Sulfasalazine	8/16 (50%)
Methotrexate	13/16 (83%)
Steroids, oral	9/16 (57%)
Steroids, intraarticular	10/16 (63%)
Steroids, intravenous	4/16 (25%)
Disease activity	
Median Tender Entheseal Count (range)	2.0 (0–8)
Median Active Joint Count	3.0 (1–17)
Erythrocyte sedimentation rate (13/16)	41.2 ± 28.6
C-reactive protein (10/16)	20.0 ± 27.9
Median C-HAQ score (9/16) (range)	0.75 (0 – 1.75)

Except where otherwise indicated, values are mean ± standard deviation.
SEA: syndrome of seronegative enthesitis and arthropathy; IBD: inflammatory bowel disease; NSAIDs: non-steroidal antiinflamatory drugs; C-HAQ: Childhood Health Assessment Questionnaire.

Outcome

Primary outcome was disease activity over time, measured clinically by TAJC and TEC at yearly time points.

Secondary outcomes were:

(i) number of patients flaring and median time to flare;
(ii) number of patients with joint replacements, time to joint replacement;
(iii) inflammatory markers at last follow-up, including CRP and ESR;
(iv) x-ray changes in the sacroiliac joint at last follow-up compared to initial imaging data, as measured by the modified New York Criteria (14);
(v) disease activity (BASDAI) at last follow-up;
(vi) functional outcome at last follow-up, including BASFI and C-HAQ/HAQ;
(vii) type of anti-TNF agents, initially and over time, length of treatment and reason for withdrawal or change of medication;
(viii) adverse events.

Statistical analysis

Baseline demographic data and treatment data were calculated using descriptive statistics. Flare-free survival was determined using the Kaplan-Meier method. Differences in characteristics and outcomes pre- and post-treatment with anti-TNF therapy were analysed by Student's *t*-test. Differences in radiographic measurements of the sacroiliac joints by New York criteria pre- and post-treatment were analysed using Wilcoxon signed-rank test. Statistical analysis was performed using SPSS statistical software (SPSS, Chicago, USA). Statistical significance was defined as a p-value of <0.05. The data are expressed as the mean ± standard deviation unless indicated otherwise.

Results

Demographics and baseline characteristics

A database search of patients with a diagnosis of juvenile SpA and treatment with anti-TNF agents in the three hospitals yielded 28 patients. Of these, 11

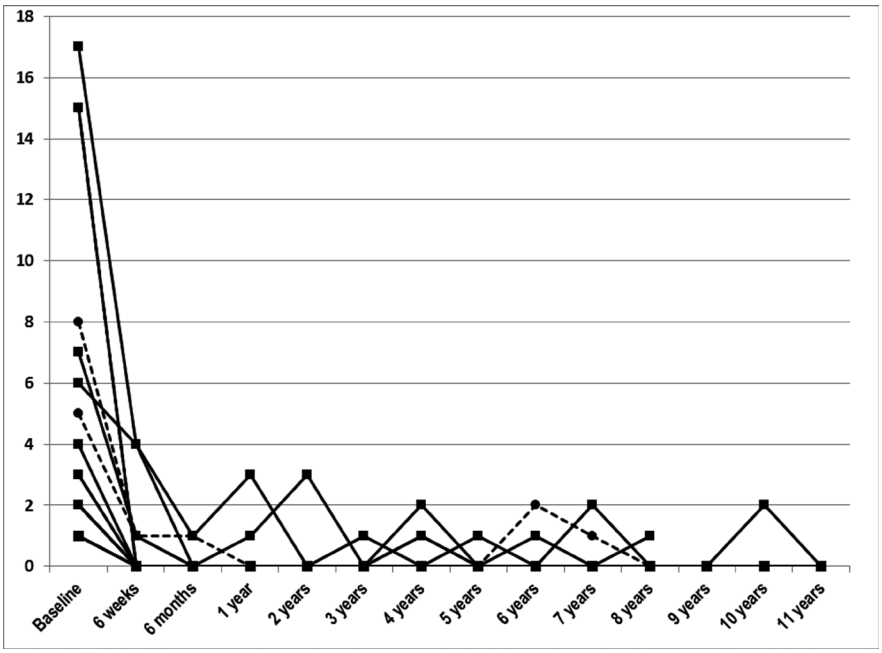

Fig. 1. Total Active Joint Count response among 16 patients with juvenile spondyloarthritis. Solid lines represent the patients receiving infliximab, broken lines represent patients receiving etanercept.

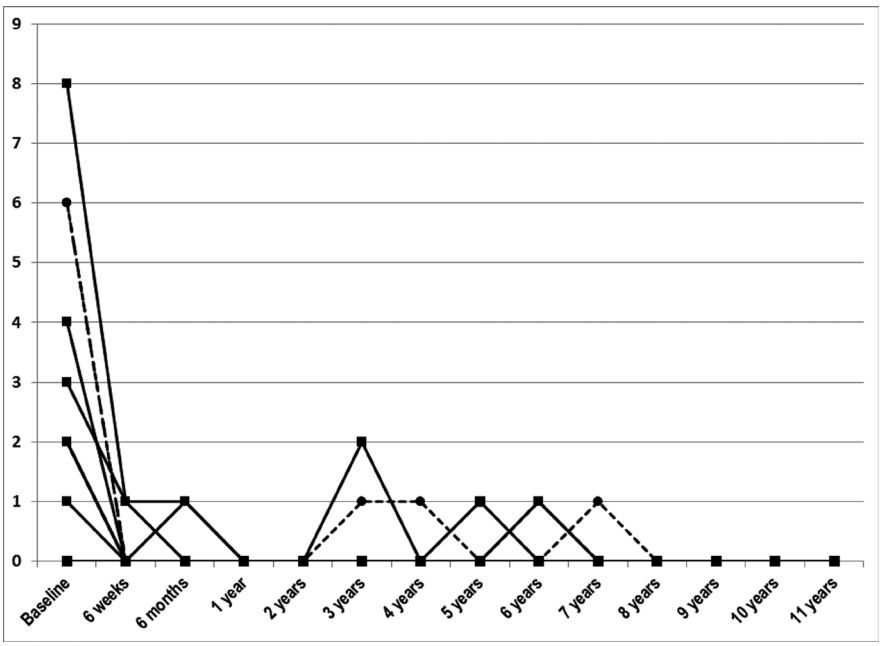

Fig. 2. Tender Entheseal Count response among 16 patients with juvenile spondyloarthritis. Solid lines represent the patients receiving infliximab initially; broken lines represent patients receiving etanercept.

patients were excluded for insufficient follow-up data or a follow-up time <2 years, and 1 patient with inflammatory bowel disease who received infliximab prior to developing arthritis.

The remaining 16 patients formed the inception cohort. Ten of these patients were previously reported with a shorter follow-up period of 1 year (9). The initial clinical features are summarised in Table I. All patients were previously treated with NSAIDs and DMARDs and had ongoing disease activity prior to initiation of anti-TNF agents. The median age at diagnosis was 11.1 years (range 6.2–15.7 years), and the median age at the start of anti-TNF therapy was 14.9 years (range 11.4–19.8 years). There were 2 female and 14 male patients, 15/16 patients (94%) were HLA-B27 positive. Mean CRP at initiation of anti-TNF treatment was 20.0±27.9 mg/L in 10/16 patients, mean ESR was 41.2±28.6 mm/h in 13/16 patients. Median C-HAQ at initiation of TNF treatment was 0.75, range 0–1.75) in 9/16 patients.

Outcome

Primary outcome: 9/16 patients (56%) achieved clinical remission with a TAJC and TEC of 0, 6 weeks into the treatment. At 6 months into the treatment, 13/16 patients (81%) had achieved clinical remission. Median time to clinical remission was 6 weeks (range 6 weeks to 2 years), only one patient required more than 1 year to achieve clinical remission. Improvement was sustained over time, with a median TAJC of 0 (range 0–3) and a median TEC of 0 (range 0–2) at any time point after 6 weeks (Fig. 1-2).

Secondary outcomes:

(i) *Disease flare*

6/16 patients (38%) showed a flare with an increase in their TAJC >0 after achieving clinical remission. Median time to flare after achieving clinical remission was 2 years (range 0.5–6.9 years) (Fig. 3). Flares involved a median TAJC of 2 (range 1–2), 2 patients also showed an increased TEC of 1 and 2 during a flare, respectively. 2 patients showed an elevated TEC of 1 without change in TAJC, not being considered a flare.

(ii) *Need for joint replacement*

2/16 patients (13%) required an arthroplasty of the hips, 3 and 8 years after initiation of treatment with infliximab, respectively. The first patient had hip disease already active prior to initiation of anti-TNF-α treatment and showed radiographic progressive disease of both hips despite continuous treatment with infliximab. The second patient had initial contact with a paediatric rheumatologist 16 month before the start of anti-TNF-α treatment, and he already was complaining about hip pain for approximately 1 year at this point.

(iii) *Inflammatory markers*
CRP at last follow-up was available in 14/16 patients and was within normal range for age in all patients (100%) with a mean CRP level of 2.3±1.5 mg/L. At last follow-up, 0/16 patients had an ESR >20 mm/hr. Mean ESR was 7.6±6.4 mm/hr.

(iv) *Radiographic evidence of sacroiliitis*
X-rays of the sacroiliac joints prior to treatment and at last follow-up were available for 12 patients. The median modified New York (NY) score for ankylosing spondylitis and grading of sacroiliitis was 1 (range 0–3) at time of diagnosis, and 3 (range 0–4) at last follow-up (p=<0.001) (Fig. 4). The percentage of patients fulfilling NY criteria prior to treatment and at last follow-up was 42% and 92%, respectively.

(v) *Disease activity*
BASDAI was determined at last follow-up for 10/16 patients, with a median BASDAI of 1.6, range 0.5–6.9.

(vi) *Physical function*
BASFI at last follow-up in 10/16 patients was determined at a median of 3.1, range 0–7.9.
The median HAQ at last follow-up was 0, range (0–1.25) for 8/17 patients.

(vii) *Ongoing requirement for anti-TNF agents*
6/16 patients (38%) were initially treated with etanercept, the remaining 10 patients were treated with infliximab. 15/16 patients (94%) were still treated with anti-TNF treatment at last follow-up. One patient discontinued treatment with infliximab after 2.75 years due to clinical remission and remains in remission at last follow-up 3 years later. One patient switched from treatment with infliximab to etanercept after three years and to adalimumab at 10 years, due to lack of efficacy with progressive hip disease. One patient each switched from etanercept and infliximab to adalimumab for lack of efficacy at 5 and 8 years, respectively, No patient switched from etanercept to infliximab.

(viii) *Adverse events*
The study represents 117.1 patient-years on treatment with anti-TNF treatment. Four patients had acute uveitis during the course of their disease, but no patient was diagnosed with any additional autoimmune disease manifestation or malignancy during the study period. One patient developed a localised njection site reaction, and one patient developed a generalised reaction, including generalised abdominal complaints and an unspecific papular rash. No patient developed any psychiatric or neurologic disorder, severe systemic infection or tuberculosis during the study period.

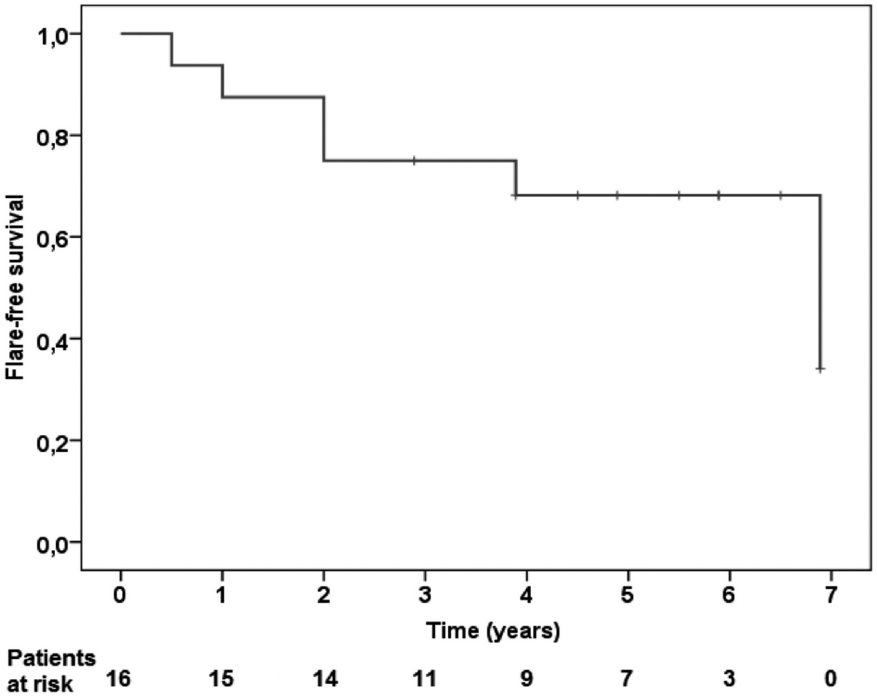

Fig. 3. Kaplan-Meyer analysis of flare-free survival of JSpA patients on anti-TNF treatment after achieving remission (n=16). Markings indicate censored patients.

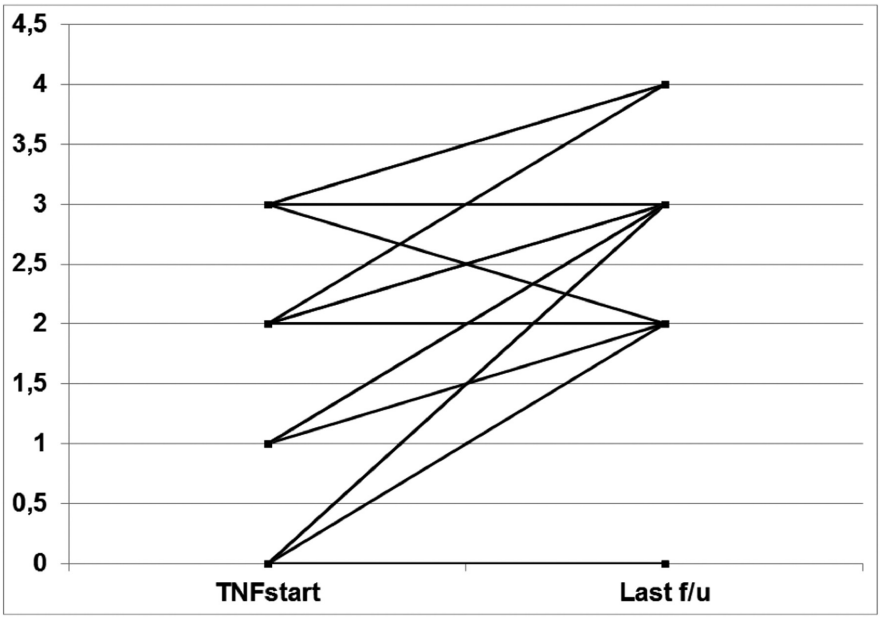

Fig. 4. Radiographic New York Scores of 24 SI joints in 12 JSpA patients before anti-TNF treatment and at last follow-up.

Discussion

This study describes the long-term outcome of treatment with biologics in

Table II. Summary of outcome parameters.

Primary outcomes	
Median tender entheseal count at last follow-up (range)	0 (0 – 1)
Median total active joint count at last follow-up (range)	0 (0 – 2)
Secondary outcomes	
Patients flaring (%)	6/16 (38%)
Median time to flare (range)	2 years (0.5 – 6.9)
Joint replacements	2/11 (13%)
C-reactive protein at last follow-up (14/16)	2.3 ± 1.5 mg/L
ESR at last follow-up	7.6 ± 6.4 mm/hr
Median BASDAI at last follow-up (10/16) (range)	1.6 (0.4 – 6.9)
Median BASFI at last follow-up (10/16) (range)	3.1 (0 – 7.9)
HAQ score at last follow-up (8/16)	0 (0 – 1.25)
Anti-TNF agent administered	
Infliximab alone	8
Etanercept alone	5
Etanercept followed by Adalimumab	1
Infliximab followed by Adalimumab	1
Infliximab followed by Etanercept, then by Adalimumab	1
Adverse events	
Uveitis	4/16
Additional autoimmune disease	0/16
Localised reactions	1/16
Generalised reactions	2/16
Neurological disorders	0/16
Psychiatric disorders	0/16
Severe systemic infection or tuberculosis	0/16

*Values given are mean ± standard deviation unless noted otherwise
**Related to age-dependent normal values
ESR: erythrocyte sedimentation rate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HAQ: Health Assessment Questionnaire.

patients with JSpA. In adult patients with SpA, increased expression of TNF-α has been reported in serum and synovium (15, 16). Increased expression of TNF-α in synovium has also been shown in various forms of JIA, most markedly in JSpA (17). Treatment efficacy has already been shown for both infliximab and etanercept in adult Ankylosing Spondylitis in large randomised controlled trials (8, 18-20). Treatment with anti-TNF-α treatments have been shown to be efficacious and safe for up to 8 years in JIA (21). However, for the subgroup of JSpA, the only published data until recently were a small trial of 10 patients and a larger trial with 53 patients with a follow-up period 1 year, demonstrating good efficacy in that time period (9, 22). A recent randomised trial in patients with JSpA has now demonstrated efficacy up to 24 weeks for adalimumab (23). The objective of this study was to describe the long-term outcome of the previously described patient cohort on anti-TNF-α treatment beyond one year of anti-TNF-α-treatment and including additional patients.

The study demonstrated that children with JSpA show an overall excellent long-term response to treatment with anti-TNF-α agents, with all patients achieving clinical remission early in the study, as reported earlier for parts of this patient cohort, and similar to other studies (9, 24, 25). 62% of patients were free of flares during the study, and the remaining 38% had mild flares with no more than two joints involved. Flares occurred late in the study, with a median time of 2 years after achieving remission. It is remarkable that all except one patient were still on anti-TNF-α treatment at last follow-up. Complete remission off medication was seen in one patient in this study, and is a rare event overall: In the Dutch cohort of mixed JIA patients on etanercept, only 8 of 147 patients discontinued the drug due to remission within an observation period of 5 years, and no ERA patient was able to discontinue treatment (25, 26). This is still better than in other studies of JSpA and long-term adult studies, where discontinuation due to remission practically does not occur (24, 27).

Two patients in this study required an arthroplasty of the hip despite long-term anti-TNF treatment. Both patients had ongoing hip disease prior to initiation of treatment. Patients with early-onset SpA not only have more frequent hip involvement compared to adult patients, but also have a demonstrated higher need for arthroplasty (28, 29). It is unclear at this point how much treatment with anti-TNF-α agents can inhibit radiographic progression of hip disease in the SpA (30). Clinicians should be aware of this limitation in anti-TNF-α treatment, and further studies are warranted. It is worthy of note that the two patients with severe hip disease also had by far the worst functional outcomes as measured by BASFI and HAQ, markedly skewing the results of the cohort.

The available radiographic data in this study also demonstrated a significant progression of sacroiliac joint arthritis in the majority of cases. Furthermore, this likely represents an underestimation of sacroiliitis as radiographic evidence often lags behind clinical disease activity. Unfortunately, more sensitive radiologic methods of assessment of the sacroiliac joints such as MRI were not available at all time points for our patients. Detection of sacroiliitis on physical exam is also variable because unlike the hip disease, which was documented as active on the physical exam during most study visits, SI joints were not reported as clinically active in almost all patients after initiation of treatment. Similarly, progression of axial disease in adult patients with ankylosing spondylitis treated with infliximab or adalimumab has been described for treatment durations up to 4 years (31, 32). Recent outcome studies on JSpA patients treated with conventional antirheumatic medications demonstrate a significant amount of functional impairment, especially affecting the hip and sacroiliac joints, compared with other forms of JIA (33-35). Considering this, the discordance between radiographic results and significant symptomatic

improvement should be acknowledged when applying current recommendations, which put anti-TNF-α agents in the forefront for active sacroiliac arthritis (10).

All patients in this study tolerated the treatment with anti-TNF-α treatment exceptionally well. The rate of acute uveitis with 25% was higher than in previously described ERA cohorts, but incidence of uveitis has been described as higher in adolescents and adults (36-38). No patient developed reactivation of tuberculosis (all patients were pre-screened), and the adverse reactions were limited to localised or non-life threatening generalised reactions. While the cohort is by far too small to comment on the risk of malignancy, in this cohort the benefits of anti-TNF-α treatment seem to outweigh the risk by a considerable margin (39, 40).

The main limitation of this study is the relatively small number of patients and the variable length of follow-up. The different medications used in this study reflect the limited choices available to the patients at the time, and the patient population was heterogeneous, including various forms of JSpA. Standardised ASAS outcome criteria could not be calculated as patient global assessments were not acquired in all cases; similarly, image data and functional assessments were not available for all patients. Nevertheless, this study represents the largest cohort of patients with JSpA with this length of follow-up and contributes valuable data on anti-TNF treatment outcome in the paediatric SpA population.

Children with JSpA treated with anti-TNF agents have an excellent and sustained response to treatment, with the notable exception of hip disease. Anti-TNF agents seem to be a safe and efficacious treatment for patients who are refractory to previous treatments with NSAIDs and DMARDs. Particular care should be taken to monitor hip and sacroiliac arthritis when using anti-TNF agents in this population, and treatment recommendations should be carefully evaluated. Randomised, controlled trials in this patient population will have to confirm the findings in this study.

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