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ORIGINAL ARTICLE

Course of patients with juvenile spondyloarthritis during 4 years of observation, juvenile part of GESPIC

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ABSTRACT

Objective: To describe the course and the 4-year outcome of juvenile spondyloarthritis (jSpA).

Methods: Patients with a diagnosis of jSpA and an age at onset ≤16 years were included in the German Spondyloarthritis Inception cohort (GESPIC) and followed up prospectively for 4 years.

Results: 118 patients (73% men, 66% HLA-B27 positive, mean age 13.5 years, mean symptom duration 2.2 years) were enrolled in 2 study centres: 52% of patients with jSpA were captured by the enthesitis-related arthritis subgroup of the International League of Associations for Rheumatology classification criteria. At inclusion, the majority of patients had active peripheral arthritis (75.4%), followed by inflammatory back pain (IBP) (19.5%) and enthesitis (16.1%). There was a significant improvement in clinical manifestations and in patient-reported outcomes over time. During the 4-year follow-up, 85% of the patients had at least 1 period of remission on drug ≥6 months, and 46% of the patients achieved remission ≥12 months without medication, of whom 68% kept this status and 32% worsened. At the end of 4 years of observation, 23% of the patients were in remission without medication, but 57% still suffered from active disease. Patients with peripheral arthritis had a likelihood of 29% for having peripheral arthritis after 4 years, whereas the likelihood of IBP persistence was 53% for those with IBP at enrolment.

Conclusions: Although 1 quarter of patients with jSpA achieved remission off medication after 4 years, the likelihood of having recurrent or persistent disease into adulthood is substantial, particularly for jSpA with IBP.

Trial registration number: NCT 01277419.

Key messages

- Our findings extend the knowledge on the disease course and outcome of juvenile spondyloarthritis under treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or disease-modifying antirheumatic drugs (DMARDs) within a specialised care.
- In patients already treated at study entry, we observed an additional improvement over time for peripheral arthritis, uveitis, the Bath Ankylosing Spondylitis Disease Activity Index and physician's global assessment of disease activity but not for pain, inflammatory back pain and function.
- The likelihood of reaching at least one episode of remission on medication was 85% and of reaching the status of remission off medication at least once was 46%.
- Our results provide guidance to physicians in counselling patients and their parents on the expected outcome of certain disease manifestations 4 years after treatment with NSAIDS or conventional DMARDs.

INTRODUCTION

Juvenile spondyloarthritis (jSpA) is a group of chronic inflammatory disease with symptom onset at 16 years of age or younger. In contrast to adult-onset spondyloarthritis (SpA), dominant clinical signs in jSpA are enthesitis and peripheral arthritis rather than inflammatory back pain (IBP).[1] Frequently, knee(s), ankle(s) and hips are affected. Boys are more frequently affected than girls, and HLA-B27 positivity, a positive family history and uveitis are also characteristics of jSpA. A minority of these patients develop ankylosing spondylitis (AS) prior to the age of 16, which is defined as juvenile-onset AS. Juvenile-onset AS differs in the first symptoms, the clinical picture, the frequency of manifestations at onset and severity in course of disease from adult-onset AS.[1–4]

The International League of Associations for Rheumatology (ILAR) developed classification criteria for juvenile idiopathic arthritis (JIA).[5] Within the JIA classification criteria, jSpA was not considered as one disease entity.[1] Most patients with jSpA fulfil criteria of enthesitis-related arthritis (ERA).

However, within the ILAR system, patients with psoriasis or a positive family history for psoriasis are excluded from the ERA group but are considered to belong to the jSpA spectrum.[1 4] For this reason and to take the concept of SpA as a group of inter-related disorders with shared clinical features into account, the European Spondyloarthropathy Study Group (ESSG) criteria[6] for adult SpA were applied in this study. The ESSG criteria have previously been shown to perform well also in juveniles with SpA.[7 8]

The knowledge on the course and the outcome of jSpA from published studies is limited.[9–22] Available studies were mainly based on JIA cohorts, and therefore, the subgroup of ERA or jSpA constituted often small subgroups in these JIA cohorts. An unfavourable outcome was reported for ERA or jSpA in most of these studies.[10 11 13 15 17 22] According to Minden *et al*,[10] only 16% of patients with jSpA achieved remission during 5 years of follow-up and more than half of the patients had active disease after ~15 years of follow-up.[11 17] Early diagnosis and treatment is important because jSpA can be a progressive disease.[23]

We used data from the juvenile arm of the German Spondyloarthritis Inception Cohort (GESPIC)[24] (clinical trials.gov NCT 01277419) to describe the course and the 4-year outcome in a larger group of patients with jSpA. GESPIC was initiated in the prebiological era to investigate prospectively the long-term outcome of early stages of AS and SpA. Juveniles and adults were included in two different subcohorts. Here, we first report on the juvenile part and describe

1. to what degree clinical signs of disease and patient-reported outcomes improved or worsened,
2. the proportion of patients who still have an active disease after 4 years of observation, and
3. the probability of an arthritis, enthesitis or IBP-free outcome in patients who suffered from these symptoms.

PATIENTS AND METHODS

Study design

GESPIC is a prospective longitudinal cohort of patients with early SpA conducted in various centres across Germany. For the juvenile arm of GESPIC, patients had to have a diagnosis of juvenile SpA according to the rheumatologist's judgement and, similar to inclusion criteria among adult patients with SpA, patients with jSpA should additionally fulfil either the modified New York criteria for AS or the ESSG criteria for SpA, the latter with minor modifications: HLA-B27, dactylitis and acute anterior uveitis were added to the list of parameters of which at least one parameter must be present.[6 25] In addition, patients had to have IBP or peripheral synovitis at study entry. Patient's age at symptoms onset had to be ≤16 years and age at study start had to be <18 years. There were no restrictions regarding disease duration or type of treatment. Patients were enrolled consecutively in 2 out of 15 GESPIC study centres between February 2002 and December 2003. These 2 centres were specialised in paediatric rheumatology only, while the remaining 13 GESPIC centres cared for adult patients only. Clinical status was assessed at baseline and every 6 months for 4 years. Informed consent was obtained from all patients and their parents. The study was performed in accordance with the Declaration of Helsinki. Ethical approval was obtained by the Ethics Commission of the Freie Universität Berlin.

Outcome assessments

Outcome assessments are based on questionnaires for patients with juvenile SpA that were completed by physicians and patients or their parents, respectively. Peripheral arthritis was defined as a joint with swelling not due to deformity or joints with loss of motion plus pain and/or tenderness. Enthesitis was assessed clinically at the iliac crest, greater trochanter, medial condyle, lateral condyle, achilles tendon and plantar fascia; additional enthesitic sites could be documented as well. Physician's global assessment of disease activity, patient's global assessment and global pain were assessed on 0–10 numerical rating scales in which higher scores indicate higher disease activity or more severe pain, respectively. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[26] was applied to measure disease activity. In a post hoc analysis, we furthermore calculated the Disease Activity Score for AS (ASDAS) with erythrocyte sedimentation rate (ESR)[27] which was developed after the start of this study. Physical function was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI, scale 0–10)[26] and by the Childhood Health Assessment Questionnaire (CHAQ)[28] ranging from 0 (no disability) to 3 (very severe disability). The Questionnaire for Measuring Health-Related Quality of Life in children and adolescents (KINDL)[29] is a German self-reported instrument. It can be analysed individually in its six dimensions (physical well-being, emotional well-being, self-esteem, family, friends and everyday functioning in school), and disease as an optional subscale, or in a total score. The KINDL ranges from 0 to 100. Higher scores indicate a better quality of life.

Remission was defined based on the Wallace criteria.[30] To consider the specific characteristics of jSpA, the criteria were modified. For inactive disease, six of the following had to be fulfilled: physician's global assessment of disease activity score of 0, no joints with peripheral arthritis, no uveitis or enthesitis, morning stiffness <15 min, no IBP and either ESR ≤20 mm/hour or C reactive protein (CRP) level ≤5 mg/L. By definition, patients who did not fulfil these criteria had active disease. We distinguished two types of remission: clinical remission on medication (defined by inactive disease for at least 6 months on medication) and remission off medication (defined by inactive disease for at least 12 months and without any medication). Assessment of SpondyloArthritis international Society (ASAS) classification criteria were assessed.[31]

In patients with IBP, imaging was intended but was rarely performed and therefore excluded from further analysis.

Statistical methods

All patients enrolled were included in the analysis. Owing to a high portion of patients with undifferentiated SpA (84%), no stratification according to specific SpA subgroups was performed.

To test whether there were changes in the clinical status over time, linear mixed models and generalised estimation equations (GEE) were used: mixed models were applied to estimate mean changes, and GEE models to estimate changes in the percentages of patients with specific clinical characteristics. For the analysis of remission, Breslow-type estimates of likelihood of achieving remission were used. The t-test and non-parametric Wilcoxon test were applied to compare HLA-B27-positive and HLA-B27-negative patients at baseline.

Patients lost to follow-up were compared with completers based on clinical data (BASDAI, pain, peripheral arthritis (yes/no), enthesitis (yes/no)) assessed at the last study visit of the dropouts and the corresponding visit of the completers. Since these comparisons did not result in significant differences (data not shown), an adjustment for a possible confounding by patients lost to follow-up was not performed. p Values of <0.05 were considered to be statistically significant.

RESULTS

SpA subgroups and classification

In total, 118 patients with jSpA were enrolled. Ninety-nine patients (84%) were diagnosed as having undifferentiated SpA, nine (8%) with reactive arthritis (ReA), seven (6%) with psoriatic-SpA (Pso-SpA) and three (2.5%) with juvenile AS. All patients fulfilled the modified ESSG criteria and three patients the modified New York criteria for AS either at enrolment or before. The classification of the patients with jSpA according to the ILAR[5] criteria system was as follows: 61 patients (52%) fulfilled the criteria of ERA, 11 (9%) for psoriatic arthritis, 10 (9%) for rheumatoid factor (RF)-negative polyarthritis, 4 (3%) for RF-positive polyarthritis, 7 (6%) for oligoarthritis and 18 (15%) were classified as cases of undifferentiated arthritis. There were seven (6%) patients with missing ILAR classification. One hundred and fifteen (97%) patients fulfilled the ASAS classification criteria.

Disease demographics and characteristics prior to and at enrolment

Seventy-three per cent of the patients were men, and 66% were HLA-B27 positive. Prior to study enrolment, nearly all of the patients ever had peripheral arthritis (96%). The most frequently affected joints were knees (77%), ankles (40%), hips (38%), toes (27%) and fingers (25%). Signs of symmetrical arthritis were observed in approximately half of the patients who had arthritis of the feet or fingers. Forty-four per cent of the patients ever suffered from enthesitis and 6–13% from psoriasis, uveitis, tarsitis or dactylitis (table 1). At enrolment, 75% of the patients suffered from peripheral arthritis, 16% from enthesitis and 20% from IBP (table 1).

Disease manifestations in relation to HLA-B27 status

HLA-B27-positive and HLA-B27-negative patients differed in physician's global assessments of disease activity (mean (SD): 2.2 (1.5) vs 1.5 (1.2); p=0.007), age, family history, CRP and ESR (table 2). In other physician and patient-reported outcomes, no significant differences were observed between HLA-B27-positive and HLA-B27-negative patients (data not shown).

Treatment and disease activity during follow-up

At enrolment, 96% of the patients with jSpA received medical therapy. There was a strong decrease in the portion of patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) and a smaller decrease in disease-modifying antirheumatic drug (DMARD) treatment over time (table 3). This resulted in a significant and clear increase in the percentage of patients who did not receive any treatment with NSAIDs, DMARDs or glucocorticoids.

Although disease activity at enrolment was an assessment under treatment in the vast majority of the patients with jSpA (96%), further significant improvements in arthritis, enthesitis, mean number of joints with limited range of motion, BASDAI, BASFI, CHAQ, patient's and physician's global assessment of disease activity were observed during 4 years of observation (table 4).

After 4 years, active disease was present in 57% of the patients: 18% had peripheral arthritis, 14% had IBP, 3% suffered from enthesitis and 9% had an ESR >20 mm/hour.

Other SpA manifestations occurred in one-fifth of the patients during the 4 years of follow-up: 13% reported dactylitis, and 6% reported psoriasis at study enrolment, which resolved completely after 4 years of follow-up. A new onset of dactylitis and tarsitis was observed in five and four patients, respectively. Psoriasis and uveitis were reported newly by three patients each. Urethritis and chronic inflammatory bowel disease were observed in one patient, and diarrhoea (more than once a month) in four patients during 4 years of follow-up.

Three patients had a diagnosis of juvenile AS at enrolment and three further patients developed juvenile AS.

Quality of life

Quality of life was assessed by the total KINDL score and its subscales which range from 0 to 100. Patients in this cohort started with a KINDL mean total score of 76 (SD=12.3). Considering the KINDL subscales at study enrolment, we found that 'family' had the highest value (mean (SD): 84 (14.3)) and 'disease' the lowest value

Table 1 Clinical characteristics ever and at study enrolment

	Juvenile SpA (n=118)	
	Clinical manifestations ever before study enrolment*	Clinical manifestations/findings at study enrolment
Peripheral arthritis, n (%)	113 (95.8)	89 (75.4)
Arthritis joint count (0–64), mean (SD)	5.1 (5.7)	2.0 (2.3)
Arthritis joint count (0–64), n (%)		
0	5 (4.2)	27 (23.3)
1	15 (12.7)	34 (29.3)
2–4	54 (45.8)	45 (38.8)
5 or more	44 (37.3)	10 (8.6)
Enthesitis, n (%)	52 (44.1)	19 (16.1)
Enthesitis count (0–12), mean (SD)	0.9 (1.4)	0.3 (0.8)
Enthesitis count (0–12), n (%)		
0	66 (56.9)	95 (84.1)
1	22 (19)	11 (9.7)
2–4	25 (21.6)	6 (5.3)
5 or more	3 (2.6)	1 (0.9)
Inflammatory back pain, n (%)	38 (32.2)	23 (19.5)
Dactylitis, n (%)	15 (12.7)	3 (2.5)
Tarsitis, n (%)	11 (9.3)	10 (8.5)
Psoriasis, n (%)	7 (5.9)	7 (5.9)
Uveitis, n (%)	8 (6.8)	3 (2.5)
CRP (mg/L), mean (SD)	–	9 (14.9)
CRP ≥5 mg/L, n (%)	–	48 (50.5)
ESR (mm/hour), mean (SD)	–	16.2 (16.4)
ESR >20 mm/hour, n (%)	–	27 (22.9)

*According to medical charts.

Table 2 Patient characteristics at study enrolment by HLA-B27 status

	HLA-B27 positive, n=78	HLA-B27 negative, n=40	p Value	All patients, n=118
Age at study start, mean (SD)	13.9 (2.5)	12.6 (2.8)	0.008	13.5 (2.7)
Male, n (%)	60 (77)	26 (65)	0.168	86 (73)
Symptom duration (years), mean (SD)	2.3 (2.1)	2.1 (1.5)	0.551	2.2 (1.9)
Duration since diagnosis (years), mean (SD)	1.6 (1.8)	1.4 (1.5)	0.788	1.5 (1.7)
Positive family history for SpA, n (%)	29 (37)	31 (78)	0.0001	60 (51)
CRP (mg/L), mean (SD)	9.8 (15.9)	7.7 (13.1)	0.001	9 (14.9)
CRP ≥5 mg/L, n (%)	40 (51)	8 (20)	0.0001	48 (50.5)
ESR (mm/hour), mean (SD)	19 (18.3)	10.9 (9.9)	0.002	16.2 (16.4)
ESR >20 mm/hour, n (%)	20 (25)	7 (18)	0.319	27 (23)

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; SpA, spondyloarthritis.

(mean (SD): 57 (12.3)). Significant improvement from study start until year 4 was observed for the subscales 'physical wellbeing' (mean (SD) from 80 (13.7) to 85 (12.3); p=0.036) and 'friends' (from 75 (17.6) to 84 (11.7); p=0.013).

Achievement of remission

The cumulative portion of patients achieving remission on and off medication is shown in figure 1A. By the end of 4 years, 85% of the patients had at least one period of remission on medication. In 49% of the remission periods on medication, treatment was terminated and remission off medication was maintained 6 months later (figure 1B), whereas 13% remained in the status of remission on medication, and 38% flared. The likelihood of achieving a status of remission off medication at least once during observation was 46% (figure 1A). The probability of remaining in this status was 68%, and that of a flare 32% (figure 1B).

Outcome at 4 years of follow-up

Using GEE models, we estimated the outcome (remission or active disease) after 4 years for all patients enrolled (n=118) and the outcome of certain disease manifestations in patients with or without such manifestations at baseline (table 5). The likelihood of having

Table 3 Treatment at baseline reflecting the past 6 months and at follow-up

Therapy	At study enrolment n=118	Month 6 n=117	Year 1 n=114	Year 2 n=104	Year 3 n=93	Year 4 n=68
No therapy, n (%)	5 (4.2)	31 (27.4)	37 (35.9)	47 (53.4)	39 (56.5)	41 (69.5)
NSAID, n (%)	101 (85.6)	78 (66.7)	60 (52.6)	38 (35.5)	25 (26.9)	16 (23.5)
csDMARD, n (%)	48 (40.7)	51 (43.6)	45 (39.5)	27 (25.2)	17 (18.3)	12 (17.6)
Methotrexate, n (%)	26 (22)	25 (21.4)	22 (19.3)	11 (10.3)	11 (11.8)	8 (11.8)
Sulfasalazine, n (%)	17 (14.4)	22 (18.8)	18 (15.8)	12 (11.2)	5 (5.4)	4 (5.9)
bDMARD (TNFi), n (%)	5 (4.2)	5 (4.3)	4 (3.5)	6 (5.6)	5 (5.4)	4 (5.9)
Combination NSAID and DMARDs, n (%)	36 (30.5)	31 (26.5)	29 (25.4)	18 (16.8)	8 (8.6)	5 (7.4)
Glucocorticoids >0.2 mg/kg, n (%)	10 (8.5)	1 (0.9)	1 (0.9)	1 (0.9)	1 (1.1)	0 (0)
Glucocorticoids ≤0.2 mg/kg, n (%)	8 (6.8)	6 (5.1)	2 (1.8)	2 (1.9)	1 (1.1)	1 (1.5)
Glucocorticoids, intra-articular, n (%)	18 (15.3)	8 (6.8)	4 (3.5)	3 (2.8)	2 (2.2)	0 (0)

bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor.

Table 4 Clinical manifestations and assessments from study enrolment until year 4

Clinical parameter*	At study enrolment n=118	Month 6 n=117	Year 1 n=114	Year 2 n=104	Year 3 n=93	Year 4 n=68	p Value
Current status							
Arthritis, n (%)	89 (75.4)	60 (51.3)	44 (38.6)	19 (17.8)	13 (14)	12 (17.6)	0.0001
Arthritis joint count (0–64), mean (SD)	2.0 (2.3)	1.3 (2.1)	1.0 (1.8)	0.4 (1.1)	0.3 (0.7)	0.5 (1.1)	0.0001
Joints with limited range of motion, n (%)	70 (59.3)	63 (53.8)	57 (50)	33 (30.8)	23 (24.7)	28 (41.2)	0.615
Joints with limited range of motion, mean (SD)	1.5 (1.4)	1.4 (1.6)	1.3 (1.4)	0.9 (1.4)	0.9 (1.6)	1.1 (1.2)	0.015
Enthesitis, n (%)	19 (16.1)	11 (9.4)	12 (10.5)	6 (5.6)	2 (2.2)	2 (2.9)	0.079
Enthesitis count (0–12), mean (SD)	0.3 (0.8)	0.1 (0.5)	0.2 (0.6)	0.1 (0.5)	0.02 (0.1)	0.1 (0.6)	0.513
Inflammatory back pain, n (%)	23 (19.7)	16 (14.5)	11 (10.9)	14 (16.9)	8 (11.9)	7 (13.7)	0.58
Patient's global assessment (0–10 NRS), mean (SD)	n.d.	2.9 (2.6)	2.1 (2.2)	2.2 (2.7)	1.8 (2.3)	2.3 (2.9)	0.006
Pain (0–10 NRS), mean (SD)	2.5 (2.3)	1.9 (2.1)	1.5 (1.8)	1.6 (2.3)	1.4 (2.1)	1.3 (1.9)	0.244
ASDAS (0–10), mean (SD)	n.d.	1.6 (0.7)	1.4 (0.7)	1.4 (0.8)	1.4 (0.8)	1.3 (0.6)	0.092
BASDAI (0–10), mean (SD)	2.0 (1.7)	1.6 (1.5)	1.3 (1.3)	1.4 (1.4)	1.1 (1.1)	1.0 (1.1)	0.002
BASFI (0–10), mean (SD)	0.7 (1.0)	0.6 (1.0)	0.4 (0.7)	0.4 (0.9)	0.3 (0.6)	0.3 (0.5)	0.002
CHAQ (0–3), mean (SD)	0.2 (0.3)	0.2 (0.4)	0.1 (0.2)	0.1 (0.3)	0.1 (0.2)	0.1 (0.2)	0.0001
KINDL (0–100), mean (SD)	76 (12.3)	77 (12.3)	79 (11.8)	80 (11.8)	81 (13.0)	82 (11.9)	0.165
Current or within the past 6 months							
Arthritis, n (%)	113 (95.8)	83 (70.9)	60 (52.6)	30 (28)	17 (18.3)	15 (22.1)	0.0001
Enthesitis, n (%)	52 (44.1)	28 (23.9)	20 (17.5)	10 (9.3)	4 (4.3)	2 (2.9)	0.0001
Inflammatory back pain, n (%)	38 (32.2)	20 (18.2)	14 (13.9)	19 (22.9)	11 (16.4)	9 (16.7)	0.495
Physician's global assessment (0–10 NRS), mean (SD)	2.0 (1.5)	1.6 (1.3)	1.4 (1.3)	1.3 (1.3)	0.9 (1.0)	1.0 (1.1)	0.0003
Uveitis, n (%)	8 (6.8)	2 (1.7)	3 (2.6)	1 (0.9)	1 (1.1)	4 (5.9)	0.07
Remission on medication, n (%)	0 (0)	6 (5.6)	10 (10.4)	21 (25.6)	23 (34.8)	23 (43.4)	0.0001
Remission off medication, n (%)	–	0 (0)	2 (2.1)	3 (3.7)	7 (10.6)	12 (22.6)	0.0004

*In the case of mean changes, mixed linear models were used to test changes over time. Generalised equation models were used to analyse changes over time for percentages.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Ankylosing Spondylitis Functional Index; CHAQ, Childhood Health Assessment Questionnaire; KINDL, Questionnaire for Measuring Health-Related Quality of Life in children and adolescents; n.d., not done; NRS, numerical rating scale.

active disease after 4 years has also been estimated according to HLA-B27 status, gender and family history (table 5).

Accordingly, we calculated a 71% chance of being arthritis-free after 4 years for patients with peripheral arthritis at baseline. The percentage of an enthesitis-free outcome for patients with enthesitis at study entry was even higher (92%). Inversely, for patients with IBP at study enrolment, there was still a 53% risk that symptoms of IBP sustained. This approach confirms that almost

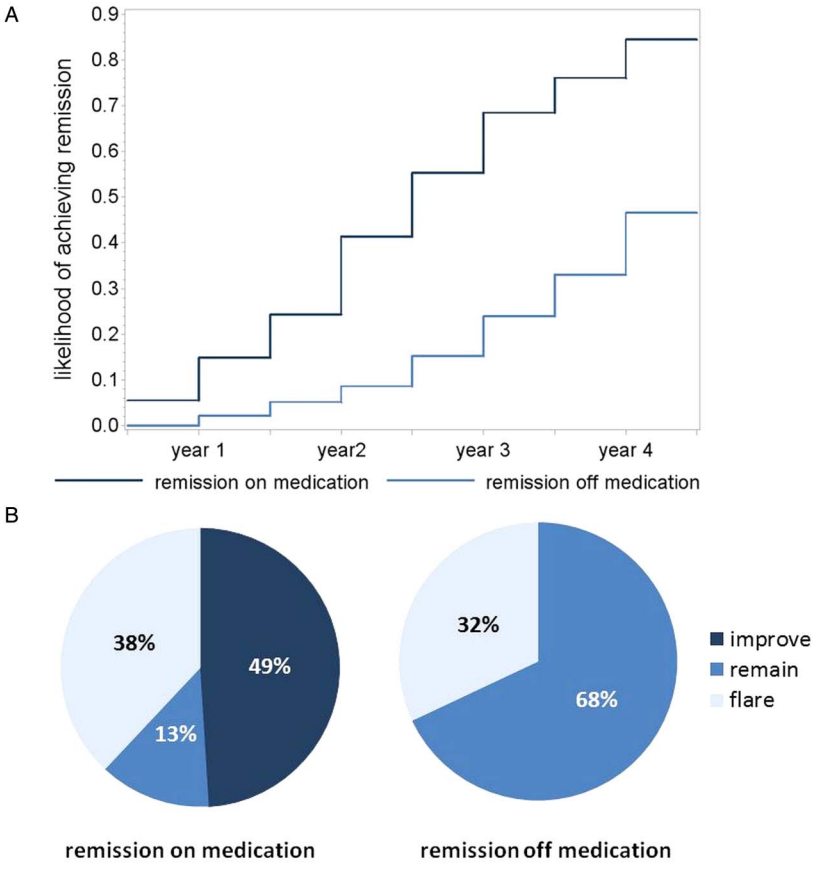

Figure 1 (A) Cumulative likelihood of achieving remission on and off medication. (B) Transition probabilities: left: transition probability of a status in remission on medication; right: transition probability of a status in remission off medication.

Table 5 Likelihood of having peripheral arthritis, enthesitis, inflammatory back pain or active disease at year 4 depending on status at study entry

Status at study entry	Status after 4 years*
Peripheral arthritis present	
Peripheral arthritis present (n=82)	29% (17%; 44%)
No peripheral arthritis (n=26)	8% (4%; 18%)
Enthesitis present	
Enthesitis present (n=18)	8% (2%; 32%)
No enthesitis (n=88)	3% (1%; 12%)
IBP present	
IBP present (n=23)	53% (31%; 74%)
No IBP (n=94)	5% (3%; 15%)
Active disease present	
All patients	54% (41%; 66%)
HLA-B27 positive (n=73)	59% (45%; 72%)
HLA-B27 negative (n=37)	42% (26%; 59%)
Male (n=79)	50% (37%; 63%)
Female (n=31)	63% (44%; 79%)
Positive SpA family history (n=57)	39% (25%; 56%)
No SpA family history (n=41)	66% (50%; 80%)

*Likelihood of a certain disease status is expressed in per cent; 95% confidence limits are shown in parentheses.

half of the patients (54%) still had an active disease 4 years after enrolment. The likelihood of having active disease was higher in HLA-B27-positive patients, women and patients without a family history of SpA.

DISCUSSION

Our prospective, 4-year observational study of patients with jSpA clearly extends the knowledge currently available from small groups of patients with jSpA as a subgroup of JIA cohorts[10 16 32] and one larger study, which, however, had to deal with a high loss to follow-up.[18] In our cohort, 85% of the patients with jSpA reached at least one episode of remission on medication during 4 years of follow-up in specialised paediatric rheumatology care. The likelihood of reaching a status of remission off medication at least once was 46%. However, these remission episodes were not stable. After 4 years of follow-up, 23% of the patients were in remission without medication; yet nearly one out of five patients had peripheral arthritis and a similar portion had IBP. In total, half of the patients had an active disease.

Guzman *et al*[18] found cumulative probabilities of attaining inactive disease in patients with ERA within 4 years of 93% which is even higher than our remission on medication rate of 85%, but our modification of the Wallace criteria was stricter, too.

Our findings agree with those of others who also found high rates of active disease in the long-term follow-up of patients with ERA or jSpA.[10 13 17] Remission rates in patients with ERA were found to be significantly lower than in patients with oligoarthritis,[10 15 17] and also lower than in patients with polyarticular JIA.[15 17 18] The low remission rates correspond to poorer physical function, more bodily pain and reduced spinal flexion in the

long term in patients with ERA compared with those with persistent oligoarticular or polyarticular JIA.[17] These remission rates may have changed recently since tumour necrosis factor inhibitors are now increasingly used in the treatment of jSpA. Treatment with these biologics played a negligible role in our inception cohort as well as in previous other studies. In one study, male sex and a positive family history were found to be associated with a poorer outcome.[15] Our data did not confirm these findings. In JIA in general, HLA-B27 positivity was found to be associated with a poorer outcome.[10 15] A similar, yet statistically non-significant, trend was seen even within the patients with jSpA in our cohort as well as in another ERA cohort.[15]

Flato *et al*[33] found that a long disease duration before first admission is a predictor of a progressive disease, a worse functional outcome and disease persistence into adulthood.[17 33] We were not able to evaluate this aspect, since we did not collect the respective information and nearly all of our patients were already treated at enrolment.

We asked whether the clinical status achieved in specialised care could further improve during the following 3–4 years, and if treatment with NSAIDs and/or DMARDs is being tapered whenever appropriate. We observed an additional improvement over time for peripheral arthritis, uveitis, BASDAI and physician's global assessment of disease activity but not for pain, IBP and BASFI. Selvaag *et al*[32] found similar results of a significant improvement in disease activity and health status but not in pain for patients with juvenile rheumatoid arthritis and jSpA during 3 years of observation. Oen *et al*[14] analysed patients with JIA within 6 months after diagnosis who were treated with a limited number of therapies, and found improvements until 6 months follow-up in peripheral arthritis, physician global assessment, patient's global assessment and CHAQ in all analysed subtypes.

Our results may provide some guidance to physicians in counselling patients and their parents on the expected outcome of certain disease manifestations 4 years after treatment with NSAIDs or conventional DMARDs. We found rather high chances for patients suffering from enthesitis or arthritis at baseline to achieve an enthesitis-free or arthritis-free status at follow-up. In contrast, there was a 53% risk that symptoms of IBP were still present 4 years later.

Klotsche *et al*[34] found that an increase in health-related quality of life on therapy with etanercept is correlated to parameters of disease activity such as pain, painful and swollen joints and ESR. To assess health-related quality of life, we used the KINDL, a German self-reported generic instrument which is accepted internationally.[35 36] The KINDL mean score at baseline was comparable to healthy adolescents.[37] During follow-up, the subscales 'physical wellbeing' and 'friends' further improved significantly, and only the subscale 'disease' worsened.

The strength of our study is the prospective study design and the large number of patients with jSpA (n=118), which is larger than those in the study by Flato *et al* (n=55)[17] and Minden *et al* (n=28),[10] and only slightly smaller than that in the study by Guzman *et al* (n=144).[18] The retention rate after 4 years was 58% in our study, which can be considered as a weakness, yet our retention rate was much higher than the retention rate of 12% in the Guzman *et al* study. We furthermore possibly underestimated the percentage of patients who developed juvenile AS at follow-up due to missing imaging data.

CONCLUSION

The results of this 4-year observation cohort in juveniles with SpA describe the disease course under conventional treatment with NSAIDs and/or DMRADs in jSpA. Major clinical manifestations such as peripheral arthritis, enthesitis or extra-articular manifestations could successfully be improved. Despite early and effective treatment, there is still a rather high risk of a (residual) active disease or disease flares during 4 years of follow-up. This risk is especially high for IBP, and much lower for peripheral arthritis and enthesitis. For these reasons, our results from the prebiological era confirm the need for new treatment options also in jSpA and the necessity for a successful transition of patients with active disease to adult rheumatology care.

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Contributors AW performed data analysis, statistical analysis, prepared tables and figures and wrote the draft manuscript. KM took care of study patients, was involved in data interpretation and manuscript preparation. JL performed statistical analysis, data interpretation and was involved in manuscript preparation. IF took care of after study patients. JS was responsible for getting funding of the trial, designed the study and was involved in manuscript preparation. MR was responsible for getting funding of the trial, designed the study and was involved in data interpretation and manuscript preparation. All authors read and approved the final manuscript.

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Course of patients with juvenile spondyloarthritis during 4 years of observation, juvenile part of GESPIC

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Notes