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Long-term outcomes in juvenile idiopathic arthritis: 18 years of follow-up in the population-based Nordic Juvenile Idiopathic Arthritis (JIA) cohort

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Abstract

Objectives: This study assessed the long-term course, remission rate and disease burden in juvenile idiopathic arthritis (JIA) 18 years after disease onset in a population-based setting from the early biologic era.

Methods: A total of 510 consecutive cases of JIA with disease onset between 1997 and 2000 from defined geographic regions in Denmark, Norway, Sweden and Finland were prospectively included in this 18-year cohort study. At the follow-up visit, patient-reported, demographic and clinical data were collected.

Results: The study included 434 (85%) of the 510 eligible JIA participants. The mean age \pm SD was 24.0 ± 4.4 years. The median juvenile arthritis disease activity (JADAS71) score was 1.5 (IQR 0-5), with the ERA category of JIA having the highest median score, 4.5 (IQR 1.5–8.5) ($P=0.003$). In this cohort, 46% still had active disease, and 66 (15%) were treated with synthetic disease-modifying anti-rheumatic drugs and 84 (19%) with biologics. Inactive disease indicated by JADAS71 <1 was seen in 48% of participants. Clinical remission off medication (CR) was documented in 33% of the participants with high variability among the JIA categories. CR was most often seen in persistent oligoarticular and systemic arthritis and least often in ERA ($P<0.001$).

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Conclusions: A high prevalence of the JIA cohort did not achieve CR despite new treatment options during the study period. The ERA category showed the worst outcomes and, in general, there is still a high burden of disease in adulthood for JIA.

SIGNIFICANCE AND INNOVATIONS

There is an ongoing debate about the long-term outcomes of juvenile idiopathic arthritis (JIA) in the biologic era. Some hypothesize that the use of biologics has improved the disease course.

This is the first study to evaluate the long-term outcomes in JIA in a population-based setting. We show that:

- 33% were in complete remission off medication
- 46% had active disease although in the mild end of the scale
- 30% received systemic treatment
- The ERA category had the worst outcomes

The study adds to the evidence that a substantial proportion of patients continue to have active disease, and the burden of medication is extensive in JIA, even 18 years after disease onset.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritides with childhood onset. Since 1999, the advent of biologics has changed the long-term functional outcome of JIA dramatically, and it may no longer be possible to rely on outcome studies from the pre-biologic era.

Whereas clinical remission on medication (CRM) now is an achievable goal for many patients with

JIA (1,2) sustained clinical remission off all antiarthritic and anti-uveitis medication (CR) is still elusive for many.

During the last two decades, the efficacy and safety of biologic therapy have been studied extensively in selected cohorts with short-term follow-up. However, the few observational studies with a long-term follow-up that have been conducted in the biologic era, are difficult to compare because of differences in the study populations (1,3,4). In recent JIA studies from the biologic era, about 21% of patients achieved CR within 5 years after diagnosis, and this proportion increased to 36% within 10 years of follow-up (5). In a population-based setting, we previously studied the 8-year outcome of all JIA categories in the very early biologic era (6). We found that about one-third still had intermittently active disease and 49% were not in remission after 8 years of follow-up. Further, 23% had developed JIA-related damage. The systemic and the oligoarticular persistent categories had the best prognosis with 80% and 65% in remission off medication, respectively.

No previous study from the biologic era was population-based or had follow-up of more than 8 years.

This study aims to add to the knowledge base by describing the long-term course, remission rate and disease burden of JIA 18 years after disease onset in a population-based setting.

PATIENTS AND METHODS

This close to population-based study followed consecutive cases of newly diagnosed JIA from defined geographical areas of Denmark, Finland, Norway and Sweden, as described previously (7). Inclusion started at disease onset between January 1st, 1997 and June 30th, 2000 (6,7). The baseline visit aimed to take place within the first 6 months (-1/+ 2 months) after disease onset. To reflect a population-based sample, the study included all consecutively referred patients from geographically defined catchment areas in each country. Letters were repeatedly sent to all primary health care centers, orthopedic, rheumatology and pediatric clinics in the catchment areas to ensure the referral of all eligible patients.

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For the 18-year follow-up, all 510 previously included participants from the Nordic study cohort were invited to participate regardless of medical exposure, disease course or activity. For participants who were unable to attend a study visit, we offered a standardized telephone interview that included electronic completion of the validated health assessment questionnaire (HAQ) (8) and visual analogue scales (VASs). Blood samples were collected from all participants that took part in the clinical study visit. The study visit included an updated family and medication history. Clinical data were collected including a joint examination and blood samples. To verify the participant reported data (e.g. in the use of determination of remission status and disease status the previous 10 years) a crosscheck of the electronic records was performed.

All participants fulfilling the ILAR criteria for JIA (9) and who had at least two study visits were eligible for inclusion in the study. There were no exclusion criteria. Approval from medical ethics committees and informed consent from all participants according to the regulations of each participating country were obtained.

Functional and clinical disease activity measures

The validated versions of the HAQ in the Nordic languages were used (8). Scores on a 21-numbered circle VAS for physician's global assessment of disease activity (PhysGA), patient-reported global assessment of well-being (PatGA) and patient-reported pain (PatPain) within the last week were collected. On this scale, 0 indicate no activity/no pain/best global health, and 10 indicate the maximum activity/worst pain/poorest global health, respectively. The composite juvenile arthritis disease activity score (JADAS71) was used (10). The JADAS71 comprises the PhysGA (range 0–10), PatGA (range 0–10), active joint count assessed in 71 joints, and the ESR (normalized to 0–10) (9). The score ranges from 0 to 101, and the cut-off value for inactive disease is 1 (11).

Definitions of inactive disease and remission

We adopted the ACR provisional criteria (12) for clinical inactive disease (CID), which includes the following: 1) No active joints; 2) no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; 3) no active uveitis; 4) normal ESR and/or CRP; 5) a PhysGA that indicates no disease activity and 6) duration of morning stiffness of ≤ 15 minutes. For CRM, the criteria for inactive disease on medication had to be fulfilled for a minimum of 6 continuous months (13). To be in CR, patients must have had inactive disease for a continuous period of minimum 12 months (13) in which they did not receive any anti-arthritis and/or anti-uveitis medication.

Articular damage and extra-articular damage were scored according to the Juvenile Arthritis Damage Indexes (JADI-A and JADI-E, respectively) (14). For the JADI-A, the score for articular damage ranges from 0 to 72. The JADI-E encompasses ocular complications, non-articular musculoskeletal damage, cutaneous features, endocrine abnormalities, malignancies and secondary amyloidosis (score ranges from 0 to 17).

Normal ESR was defined as a velocity below 20 mm per one hour, and a normal CRP level as below 10 mg/L (15). Immunofluorescent ANA tests using HEp-2 cells were performed using cut-off values for ANA as defined by the individual laboratories at each center.

Statistical analysis

Descriptive statistics of mean and standard deviation (SD) or median and interquartile range (IQR) were used to assess the clinical characteristics and disease activity of the cohort. The chi-squared or Fisher's exact tests were conducted as appropriate, to compare categorical data. The Mann-Whitney test and Kruskal-Wallis test was used to compare medians for ordinal data.

RESULTS

Study population

This study included 434 (85%) of the 510 eligible participants with JIA onset from 1997 to 2000. The follow-up period was 17.5 ± 1.7 years (mean \pm SD) after onset. The mean age of the study participants was 24.0 ± 4.4 years (Table 1); 329 (76%) participants attended a follow-up visit, and 105 (24%) were evaluated via telephone interview (Fig 1). At the 18-year follow-up the distribution among the JIA categories was: 3.2% systemic, 27.4% persistent oligoarticular, 19.6% extended oligoarticular, 16.4% polyarticular RF negative, 1.4% polyarticular RF positive, 6.5% psoriatic, 10.4% enthesitis-related arthritis (ERA) and 15.2% undifferentiated JIA (Table 1).

At the time of inclusion, only 24/434 (6%) were followed at the pediatric clinics, 148/434 (34%) were followed by adult rheumatologists and 58% did not have any clinical follow-up owing to their JIA.

Of the 76 individuals that were lost to follow-up, one died, 7 declined participation and in 68 cases the reason was inability to contact them. A comparison of the 76 (15%) participants lost to follow-up versus participants included in the follow-up study showed no differences in sex, age at onset, number of active joints during the first 6 months after onset, JIA category, CHAQ or JADAS at baseline (data not shown). Comparing participants assessed by telephone interview (subjective remission) versus participants who underwent clinical examination, the chance of being in remission off medication at the last follow-up was twice as high as for those assessed by telephone interview ($P<0.001$).

Disease activity and damage

For participants who underwent clinical examination at the 18-year follow-up study, the median active joint count was 0 (IQR 0–0). The median cumulative active joint count from inclusion to last follow-up was 8 (IQR 4-15) (Table 2). The median PhysGA of disease activity was 0 (IQR 0-1) and the

PatGA for the overall well-being was 0.5 (IQR 0-2.5). The distribution of scores differed significantly between the JIA categories (Table 1). Few participants had elevated inflammatory markers (Table 1).

Overall, the median JADAS71 was 1.5 (IQR 0-5) (Table 2), and 48% of the patients had a JADAS71 score <1.

Morning stiffness more than 15 minutes of duration was found in 67/385 (17%) with the lowest proportion in the persistent oligoarticular category (P=0.02). We found 19 cases where the only variable indicating active disease was patient-reported morning stiffness of more than 15 minutes (Table 4) and they were dispersed in all JIA categories except systemic JIA.

Articular damage (JADI-A) was seen in 65 (19.8%) of patients at the follow-up visit, while 41 (12.5%) had developed extra-articular damage (JADI-E). Ocular damage was the most common extra-articular damage and was observed in 26/329 (7.9%) of the participants. The polyarticular RF negative and psoriatic categories had the highest JADI-A and JADI-E scores (Table 2).

Medication

Treatments in the first median 12 months after disease onset are listed in table 3. Anytime during the disease course 59.7% had been treated with synthetic disease-modifying anti-rheumatic drugs (DMARDs) and 29.5% of the participants had been treated with biologics (Table 3). Participants with ERA had most often been treated with biologics (23/45 (51%)), and DMARDs were most often used in polyarticular RF negative participants (62/71 (87%)).

In total, 189/434 (43.5%) participants had not received any anti-rheumatic treatment in the preceding 10 years and the distribution across the JIA categories was: systemic 12/14 (86%); persistent oligoarticular 85/119 (71%); extended oligoarticular 19/85 (22%); polyarticular RF negative 19/71 (27%); polyarticular RF positive 3/6 (50%); psoriatic 9/28 (32%); enthesitis-related

arthritis (ERA) 13/45 (29%) and undifferentiated JIA 29/66 (44%). Within the preceding year, 12% had received at least one intra-articular corticosteroid injection (IACI).

At the last follow-up visit 128/434 (29.5%) participants were taking DMARDs (20.0%), biologics (19.2%) and/or oral corticosteroids (2.8%)(Table 3). Methotrexate was the most frequently used drug, taken by 57 (13.1%) of the participants. At the last visit the proportion of participants with ERA (17/45, 37.8%) taking biologics was significantly higher than in the other JIA categories (P=0.01).

Within the preceding year, 12% of the total cohort had received at least one intra-articular corticosteroid injection (IACI).

Assessing disease status at the study visit revealed that 131 (39.8%) participants had active disease of whom 6 (4.6%) were currently taking DMARDs as monotherapy, 46 (35.1%) were taking biologics and 30 (22.9%) were taking a combination of DMARDs and biologics. Of all the participants who still had active disease, 49 (37.4%) were not taking any medication.

The main reason for “active disease” was an active joint count of 1. In 9 of the cases the active disease was due to morning stiffness (>15 min) as an isolated finding of active disease. In two participants active disease was due to unrecognized uveitis flare detected at the FU visit and furthermore, two patients reported that medication had been prescribed but they refused to take it.

Remission

Evaluable for the remission status according to the Wallace criteria were the 329 participants of the cohort that attended a clinical visit. The medical history including the treatment within the previous year was cross-checked with the information in the records for the majority of the participants (301/329; 91%). At the final follow-up visit we found that 150 (45.6%) had active disease and did not fulfil the ACR provisional criteria for inactive disease 12 (Table 4). Active disease was observed in all categories (Fig 2). The vast majority of participants with active disease (75.4%) had normal ESRs. The

proportion with active disease in the ERA category was 64.9%, the highest proportion found in all the categories (Fig 2) even though biologic medication was most frequently used in ERA (37.8%).

More than half of the participants with psoriatic arthritis had active disease, while only 3 (10.7%) were on biologics (data not shown). If morning stiffness ≤ 15 minutes was not included as a criterion for inactive disease as in Wallace' preliminary 2004 criteria, only 131 (39.8%) participants would have qualified for an active disease status (Table 4).

Complete remission off medication (CR) was observed in 108/329 (32.8%) of the participants who had a clinical examination at the last follow-up (Table 4). Another 33 participants (10%) were in remission on medication for at least 6 months and 38 (11.6%) were having inactive disease although not yet fulfilling Wallace' preliminary remission criteria with respect to the duration of inactive disease. The persistent oligoarticular and systemic JIA categories had the highest proportions of CR (54.2% and 53.8%, respectively) and the lowest proportion of CR was found in the ERA category (8.1%) being significantly lower than in the other categories (Fig.1, $P < 0.001$).

If we included the telephone-interviewed participants and accepted the participants' own judgement of having inactive disease, the proportion of CR was 186/423 (44.0%) (Table 4).

DISCUSSION

To date, this is the largest close to population-based study to investigate the long-term outcome in JIA in the transition from pre-biologic to biologic era. In the Nordic countries biological therapy was introduced in 1999 and 2000, which means that for most of the patients included in this study biologics were not available at the very beginning of their disease course. Although 94% were no longer followed at the pediatric departments we were able to include 85% of this prospectively included, non-selected JIA cohort 18 years after disease onset, and more than three quarter of the participants were evaluated by clinical examination and blood tests.

Our results confirm the conceptual knowledge of JIA as a chronic disease since only 33% of the JIA participants were in complete remission for at least 12 months off medication (CR) 18 years after disease onset. Further, more than 45% of the cohort had active disease even 18 years after disease onset. However, our results show that the vast majority of patients with active disease were in the very mild range of the activity scale and many of the patients even had such a mild disease activity that medication was considered unnecessary.

Disease status varied extensively according to the JIA categories. CR was most often seen in participants with persistent oligoarticular and systemic JIA and was least often seen in ERA.

As a comparison, Selvaag et al. reported a higher number of participants in CR (59%) and fewer with active disease (34%) in their 30-year prospective, longitudinal follow-up study in Norway from the pre-biologic era (3). However, only half of the participants underwent clinical examination selected from an initial questionnaire if they were on medication or had patient-reported signs of disease activity. It is conceivable that the high number of participants not evaluated clinically would have increased the rate of CR as this was also the case for the group of participants in our study that were evaluated by telephone interview. Selvaag et al. also reported that the systemic and oligoarticular category of JIA had the highest remission rate; and as in our study, the lowest remission rate was seen in the RF positive polyarticular and the ERA categories.

Bertilsson and colleagues conducted a population-based cohort study in the pre-biologic era and found that 17 years after disease onset, only 2% of the participants had active disease, while 40% were in remission. However, this study used the European League Against Rheumatism (EULAR) diagnostic criteria for Juvenile Chronic Arthritis (JCA) and RA disease activity/remission criteria (16).

In our study 29.5% of the participants remained on DMARDs and/or biologics at follow-up, indicating that there is still a high disease burden even 18 years after disease onset. This is consistent with the findings of Bertilsson et al. (17), showing that 24% of the participants were on DMARDs after 17-year follow-up.

We applied the 2011 ACR definition of CID (12), which includes morning stiffness and found that in 6% of the cohort with active disease, this disease status was exclusively based on morning stiffness.

This variable may indicate some level of disease activity not captured by the physicians or blood samples in adult JIA patients. Taking morning stiffness into account in contrast to the preliminary Wallace criteria (13) have skewed our data towards a higher proportion with active disease.

Although, the role of morning stiffness in disease activity has been debated in previous reports in RA patients (18,19) we found that baseline morning stiffness is an important predictor of not being in remission 8 years after disease onset (20). However, it is important to acknowledge that there are insufficient data to optimally measure morning stiffness and its role in the spectrum of CID and remission in RA, and data on adult JIA patients has not been studied (21,22).

Unexpectedly, only 42% were followed by a physician or rheumatologist although almost 46% had active disease at last follow-up. This indicates that some of the participants might be lost to follow-up after transfer to adult care even in government-funded health care systems with minimal out-of-pocket co-payments.

To our surprise 37% of the participants with active disease did not receive any systemic treatment. Of these, 19% had morning stiffness more than 15 minutes, which was registered as the only sign of active disease and was deemed not requiring any systemic treatment. In two other cases it was due to unrecognized flare of their uveitis, and furthermore few participants had medication prescribed but did not take it. One might think that minor disease activity such as a flare with synovitis only in a knee would preferably be treated with an intra-articular corticosteroid injection rather than with systemic treatment.

When looking back at the treatment during the preceding 10 years more than 40% had not received any anti-rheumatic treatment indicating that the disease was not present anymore. This was least often observed in the extended oligoarticular category.

The strength of our study is its population-based setting and its prospective design enabling us to

evaluate long-term outcome in a non-selected JIA cohort. The percentage of participants lost to follow-up is acceptable (15%) and is less than in other long-term outcome studies (3,17). We used validated outcome measures, and the entire cohort was invited to attend a clinical visit regardless of disease status with a high proportion of respondents. Further, the genetic variability of the participants in this study is rather low with >95% being Caucasians.

For the achievement of an inactive disease status end-scale avoidance may play an important role when reporting the PhysGA, skewing the score towards a more active disease course. This challenge has also been addressed by Filocamo et al. (23) and other studies have used PhysGA <10 mm as the lower limit of inactive disease to avoid the skewness (1,24).

One limitation of this study may be the validity of data collected by telephone interview. For this reason, we chose to report remission data for participants that attended a clinical visit separately in order to improve the validity of the data. We found significantly more participants in remission (subjective remission) based on participant's answers by telephone survey compared to CR in the group attending a clinical visit ($P < 0.001$). This is an uncertain measure, as we do not have a joint count and inflammatory biomarkers (ESR) from individuals participating in the telephone survey only. Nevertheless, one could speculate that specifying the disease status exclusively among the participants attending a clinical visit has skewed the remission data for that group towards worse outcomes.

Still, 65% of the eligible cohort was evaluated by clinical examination compared to 35% in a previous Norwegian study (2).

JIA has a fluctuating disease course, and it is a limitation of our study that we did not report data between 8 and 18 years of follow-up. In addition, the inclusion period was at the very beginning of the biologic era (25), indicating that few of the participants received early biologic treatment.

Treatment guidelines (26,27) have changed during the last two decades, but there is still a need for validated instruments to standardize the concept of early aggressive therapy (28). Although the

treatment traditions among the centers in the Nordic countries are fairly homogeneous, it cannot be excluded that individual interpretations of treatment strategies of the participating centers might have affected the long-term outcomes.

In summary, this study found a substantial prevalence of ongoing active disease and a high burden of medication and damage in JIA even 18 years after disease onset. Notably, the ERA category of JIA had the worst outcomes in terms of JADAS score, remission rate and medication use.

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FIGURE LEGENDS

Figure 1 Flow-chart of the study population. F=female, M=male.

Figure 2 Disease status in JIA 18 years after disease onset (n=329).

Systemic, systemic juvenile idiopathic arthritis; Oligoarticular persist, persistent oligoarticular; Oligo ext, extended oligoarticular; PolyRF pos, polyarticular RF positive; PolyRF neg, polyarticular RF negative; Psoriatic, psoriatic arthritis; ERA, enthesitis-related arthritis; Undiff, undifferentiated JIA. * $p < 0.0001$, Remission off medication (CR) in ERA participants compared to the other JIA categories.

Table 1 Clinical characteristics of participants in the Nordic JIA cohort at the 18-year follow-up visit.

	Assessed patients, n	Total cohort	Systemic	Oligo persistent	Oligo extended	Poly RF-	Poly RF+	Psoriatic	ERA	Undifferentiated
n (%)		434	14 (3.2%)	119 (27.4%)	85 (19.6%)	71 (16.4%)	6 (1.4%)	28 (6.5%)	45 (10.4%)	66 (15.2%)
Females, n (%)	434	297(68.4)	9 (64.3)	79 (66.3)	67 (78.8)	52 (73.2)	5 (83.3)	20 (71.4)	14 (31.1)	51 (77.3)
Age at onset, years	432	6.5±4.1	6.5±4.5	5.7±3.7	4.9±3.7	5.7±4.0	11.1 ±2.1	7.3 ±4.2	9.4±3.6	7.8±4.2
Age at follow-up, years,	434	23.9 ±4.4	24.6 ±4.6	23.5 ±4.0	22.4 ±4.0	22.9 ±4.4	28.7 ±1.8	25.1 ±4.5	26.9 ±4.0	24.6 ±4.6
Disease duration, years,	431	17.5 ±1.7	18.0 ±0.7	17.7 ±1.1	17.5 ±1.4	17.2 ±1.2	17.8 ±0.9	17.4 ±1.0	17.5 ±2.5	17.2 ±2.7
CRP >10 mg/L, n (%)	328	16 (4.9)	0 (0.0)	2 (2.7)	3 (4.8)	3 (5.0)	0 (0.0)	2 (8.3)	4 (10.5)	2 (3.8)
ESR >20 mm/h, n (%)	282	19 (6.7)	0 (0.0)	3 (5.0)	3 (5.5)	3 (5.5)	0 (0.0)	3 (12.5)	4 (12.5)	3 (7.0)
ANA positive, n (%)	303	92 (30.4)	3 (27.3)	18 (26.9)	22 (39.3)	16 (28.1)	2 (50.0)	6 (24.0)	9 (25.0)	16 (34.0)
HLA-B27 positive, n (%)	409	93 (22.7)	2 (15.4)	12 (11.1)	10 (12.7)	10 (14.1)	1 (16.7)	5 (18.5)	35 (79.5)	18 (27.3)
PhysGA VAS, median (IQR)	328	0 (0–1.0)	0 (0–0)	0 (0–0)	0 (0–1.5)	0 (0–1.0)	0 (0–2.0)	0 (0–1.0)	1.0 (0–2.5)	0 (0–2.0)
PatGA VAS, median (IQR)§	404	0.5 (0–2.5)	0 (0–0.5)	0 (0–1.5)	0.8 (0–2.5)	0.5 (0–2.3)	1.5 (0–5.5)	1.0 (0–2.5)	1.5 (5–4.0)	1.0 (0–4.0)
PatPain VAS, median (IQR)§	404	0.6 (0–3.0)	0 (0–0.5)	0 (0–1.5)	1.0 (0–4.0)	1.0 (0–27.5)	2.0 (0–6.0)	0.5 (0–4.0)	1.0 (0–3.0)	1.5 (0–4.0)
Morning stiffness ≥ 15 min., n (%)	385	67 (17.4)	0 (0.0)	6 (6.0)	13 (16.5)	12 (18.5)	2 (33.3)	5 (23.8)	13 (33.3)	16 (25.8)

The second column shows the number of patients that were assessed at the final study visit. Age and disease duration are expressed as mean of years \pm SD. PhysGA VAS, physician global assessment of disease activity on a visual analogue scale; PatGA, patient global assessment of overall well-being; PatPain, patient reported rating of intensity of pain. §Statistically significant differences between JIA categories; P=0.015 for PatPain and P<0.001 for PatGA. IQR, 1st -3rd interquartile range.

Table 2 Disease activity and damage observed in participants in the Nordic JIA cohort at the 18-year follow-up visit.

	Number assessed	Total cohort	Systemic	Oligo persistent	Oligo Extended	Poly RF-	Poly RF+	Psoriatic	ERA	Undifferentiated
n (%)		329(100%)	13 (4.0%)	72 (21.9%)	66 (20.1%)	59 (17.9%)	5 (1.5%)	22 (6.7%)	37 (11.2%)	55 (16.7%)
Active joint count	329	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-1)	0 (0-0)
Cumulative joint count	329	8 (4-15)	7 (4-12)	2 (1-3)	8.5 (7-11)	14.0 (8-24)	17 (15-20)	8.5 (5-12)	10 (5-18)	10 (3-25)
Joints with LOM	329	0 (0-1)	0 (0-0)	0 (0-1)	0 (0-2)	0 (0-3)	0 (0-1)	0 (0-2)	0 (0-2)	0 (0-1)
JADAS71*	294	1.5 (0-5)	0 (0-0.5)	0 (0-3)	2 (0-4.5)	1 (0-4.0)	2.5 (0-9.5)	2 (0-4.8)	4.5 (1.5-8.5)	2.0 (0.3-9.0)
JADAS71 ≤1**	294	142 (48.3)	9 (81.8)	39 (62.9)	26 (44.1)	34 (60.7)	2 (40.0)	7 (35.0)	8 (24.2)	17 (35.4)
HAQ	404	0 (0-0.1)	0 (0-0)	0 (0-0)	0 (0-0.1)	0 (0-0.2)	0.1 (0-1.4)	0 (0-0.3)	0 (0-0.3)	0 (0-0.3)
HAQ >0, n (%)	404	114 (28.2)	2 (15.4)	17 (15.9)	23 (28.8)	21 (30.9)	3 (50.0)	9 (36.0)	16 (39.0)	23 (36.5)
JADI-A >0, n (%)	329	65 (19.8)	2 (15.3)	5 (6.9)	13 (15.3)	23 (39.0)	0 (0.0)	5 (22.7)	5 (13.5)	12 (21.8)
JADI-E >0, n (%)	329	41 (12.5)	1 (7.7)	9 (12.5)	7 (10.6)	12 (20.3)	0 (0.0)	5 (22.7)	4 (10.8)	3 (5.5)

Values are expressed as median (1st -3rd interquartile range (IQR)), unless otherwise expressed. The second column indicates the number of patients that were assessed at the final clinical visit. LOM, limitation on motion, ERA, enthesitis-related arthritis, *JADAS71, juvenile arthritis disease activity score based on evaluation of 71 joints, **JADAS71 ≤1 indicates inactive disease according to Consolaro et al (13). JADI-A, Juvenile Arthritis Damage Index-articular; JADI-E, Juvenile Articular Damage Index-extra-articular.

Table 3 Status of the medical therapy according to JIA category in the Nordic JIA cohort at the 18-year follow-up visit.

	Total cohort at last FU n=434	Systemic n=14	Oligo persistent n=119	Oligo extended n=85	Poly RF- n=71	Poly RF+ n=6	Psoriatic n=28	ERA n=45	Undifferentiated n=66
DMARDs 1st year* (n=341)	125/341 (36.7)	9/13 (69.2)	30/167 (18.0)	7/12 (58.3)	49/70 (70.0)	3/5 (60.0)	1/6 (16.7)	10/23 (43.5)	16/45 (35.6)
Biologics 1st year*(n=6)	6/341 (1.8%)	0/13 (0.0)	0/167 (0.0)	1/12 (8.3)	2/70 (2.9)	2/5 (40.0)	0/6 (0.0)	1/23 (4.3)	0/45 (0.0)
DMARDs ever	259 (59.7)	11 (78.6)	28 (23.5)	64 (75.3)	62 (87.3)	4 (66.7)	18 (64.2)	33 (73.3)	39 (59.1)
Biologics ever	128 (29.5)	3 (21.4)	13 (10.9)	28 (32.9)	31 (43.7)	2 (33.3)	10 (35.7)	23 (51.1)	18 (27.3)
Monotherapy DMARDs** at last FU	41 (9.4)	0 (0.0)	7 (5.6)	9 (10.6)	11 (15.5)	1 (16.7)	5 (17.9)	4 (22.5)	4 (6.1)
Monotherapy biologics*** at last FU	38 (8.8)	0 (0.0)	3 (2.5)	8 (9.4)	6 (8.5)	1 (16.7)	2 (7.1)	9 (20.0)	9 (13.6)
Biologics + DMARDs at last FU	46 (10.6)	2 (14.3)	4 (3.4)	11 (12.9)	16 (22.5)	0 (0.0)	1 (3.6)	8 (17.8)	4 (6.1)
Systemic corticosteroids at last FU	12 (2.8)	0 (0.0)	1 (0.8)	1 (1.2)	6 (8.5)	0 (0.0)	0 (0.0)	3 (6.7)	1 (1.5)
No medication at last FU****	306 (70.5)	12 (85.7)	103 (86.6)	59 (69.4)	39 (54.9)	4 (66.7)	23 (82.1)	22 (48.9)	49 (74.2)
Joint injection within the last year	52 (12.0)	0 (0.0)	7 (5.9)	15 (17.6)	11 (15.5)	0 (0.0)	3 (10.7)	6 (13.3)	10 (15.2)

Values indicate the number of patients, with percentage in brackets. FU, follow-up. ERA, enthesitis-related arthritis. * The disease-modifying antirheumatic drugs (DMARDs) and biologics used during median 12 months after onset in the categories at that time point. **DMARDs included methotrexate, azathioprine, hydroxychloroquine, leflunomide, sulfasalazine and mycophenolate mofetil. ***The biologic drugs included etanercept, infliximab, adalimumab, certolizumab, golimumab, rituximab, abatacept, anakinra, canakinumab, riloncept and tocilizumab. ****Off all systemic treatment (DMARDs, biologics and steroids).

Table 4 Remission status of participants attending a clinical visit and/or including the interviewed participants in the Nordic JIA cohort at the 18-year follow-up based on Wallace’s preliminary and ACR provisional criteria for the definition of inactive disease.

	According to the preliminary criteria ¹³ (visit)	According to the ACR provisional criteria ¹² (visit)	According to the preliminary criteria ¹³ (visit + interview)
Active disease	131 (39.8±5.3)	150 (45.6±5.4)	140 (33.1±4.5)
Remission on medication	37 (11.2±5.4)	33 (10.0±3.2)	40 (9.5±2.8)
Remission off medication	116 (35.3±5.2)	108 (32.8±5.1)	186 (44.0±4.7)
Inactive disease, not yet in remission*	45 (13.7±3.7)	38 (11.6±3.5)	57 (13.5±3.3)
Assessed participants	329	329	423

Values in brackets are expressed as percentages of each subcategory with 95% CI.

* Inactive disease, but not fulfilling the remission criteria.



