Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis

Anne M Selvaag,1 Hanne A Aulie,1 Vibke Lilleby,1 Berit Flato1,2

ABSTRACT

Objectives To describe disease activity 30 years after disease onset in a previously studied cohort of patients with juvenile idiopathic arthritis (JIA) and reveal predictors of long-term active disease.

Methods Patients with JIA, first referred 1980–1985 and re-examined 15 and 23 years after onset, were invited to attend. All 176 patients were assessed by questionnaires. Patients with signs of active disease at 15 years or later also came to a clinical re-examination (n=90). Disease activity was assessed by the clinical juvenile arthritis disease activity score (JADAS3) and by the criteria for remission in JIA, and health status by Health Assessment Questionnaire (HAQ) and Medical Outcome Study 36-item Short Form Health Survey (SF-36).

Results At 30-year follow-up, 59% of the patients were in clinical remission off medication, 7% were in remission on medication and 34% had active disease. 70% of the patients were in the same category of disease activity at 15 and 30 years. The JADAS3 was ≤2.0 in 54%, 2.1–4.5 in 18% and >4.5 in 28%. HLA-DRB1*01, physician’s global assessment and a short total time in remission at 15 years, predicted active disease. Physician’s global assessment also predicted a JADAS3 >4.5. From 15 to 30 years (n=90), physician’s global assessment, number of active joints, erythrocyte sedimentation rate and C reactive protein improved significantly, but patient’s global assessment, HAQ and SF-36 did not.

Conclusions 41% of the patients with JIA had active disease or were on medication after 30 years and 28% had a high symptom state. Remission rates and patient-reported health status at 15 years were comparable with rates at 30 years.

INTRODUCTION

The disease activity in juvenile idiopathic arthritis (JIA) can persist for many years, even through adulthood, but may also go into remission with minimal sequelae before the patient reaches adulthood.

Follow-up studies of patients with JIA of more than 20 years are scarce, and previous long-term studies of JIA are difficult to compare due to different definitions of remission and disability.1–4 Few long-term studies have included the recently developed criteria for remission in JIA and longitudinal assessments of health status.5

In adult rheumatology, pooling of disease activity measures into composite scores has resulted in scores like the Disease Activity Score in 28 Joints.6 Recently, a similar instrument, the Juvenile Arthritis Disease Activity Score (JADAS), was evaluated for JIA.7 Several studies have implemented this instrument, but it has not previously been used in a long-term follow-up study.

The aim of this study was to assess disease activity and health status in a previously studied cohort of patients with JIA 30 years after disease onset, to compare disease activity after 15 and 30 years and to reveal predictors of long-term active disease.

MATERIALS AND METHODS

Patients and controls

A total of 260 patients with JIA, first time referred to Oslo University Hospital, Rikshospitalet, from 1980 to 1985, were re-examined clinically after median 15 years of disease duration and by mailed questionnaires after median 23 years.7–9 Six patients had died, thus 254 patients were invited to take part in the present study. All patients were assessed by questionnaires and those with signs of active disease and/or on antirheumatic medication after 15, 23 and/or 30 years were invited to an extended clinical examination.

The patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria for JIA after 15 years of disease duration.10 11 Disease onset was defined as the day the physician diagnosed the arthritis.

Informed consent was obtained from all the participants.

Clinical examination

The patients were examined by one of the three rheumatologists at follow-up (BF, VL and AMS). The clinical examination included registration of number of joints with swelling, tenderness and limited range of motion (LROM), number of active joints (swelling or both tenderness and LROM) and physician’s global assessment of disease activity (on a five-point Likert scale, where one means inactive and five very severe disease activity, and on a 10 cm visual analogue scale (VAS), where 0 means no disease activity and 10 means very severe disease activity).

Remission, medication and health status

Inactive disease was defined according to the preliminary criteria for clinical remission in JIA, as having no active arthritis; no fever, rash, serositis, splenomegaly or generalised lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate (ESR) or C reactive
protein (CRP); and a physician’s global assessment of disease activity rated at the best score possible for the instrument used, except that for patients in remission off medication after 15 years, inactive disease was defined as no history of flare after 23 and 30 years. Clinical remission on medication was defined as minimum six continuous months of inactive disease on medication. Clinical remission off medication was defined as minimum 12 months of inactive disease off all antiarthritic and antiuveitis medication. All the patients received a questionnaire about antirheumatic and antiuveitis medication, history of joint injections, presence of uveitis, quality of life according to the Medical Outcome Study 36-item Short Form Health Survey (SF-36) and physical disability and discomfort assessed by the Health Assessment Questionnaire (HAQ). A cut-off value for an acceptable symptom state has been found to correspond to a JADAS <4.5 for children with JIA. We, therefore, chose a JADAS >4.5 as a level of a high symptom state.

Statistical analyses

The differences between participants and non-participants and between two patient groups were analysed by t tests for continuous data and by χ² tests for categorical data and frequencies. Because of non-normality distribution we used Kruskal–Wallis test to analyse differences in the JADAS3 across the JIA categories and Mann–Whitney U tests to reveal differences between two independent groups (results with a p<0.01 were reported because of multiple comparisons). Spearman’s correlation coefficient was used to assess the relationship between the JADAS3 and categories of disease activity. We used Wilcoxon signed-rank test for comparisons between continuous non-normality distributed data from 15-year and 30-year follow-up, and Friedman’s two-way analysis of variance for more than two comparisons.

Logistical regression analyses were used to assess predictors of active disease and a JADAS3 >4.5 (see online supplementary text).

For all analyses, p values <0.05 (two-tailed tests) were considered statistically significant. All analyses were performed on the SPSS software programme (SPSS, Chicago, Illinois, USA) V18.0.

RESULTS

Patient characteristics

Out of 254 eligible patients, 176 (69%) were assessed by questionnaires after median 29.6 years (range 20.6–39.9) of disease duration. The median age was 38.8 years (range 27.8–45.1) and 74% were women. Ninety patients also came to a clinical examination.

The 176 participants were comparable with the 84 non-participants (including six deceased patients) with regard to gender, disease category and disease duration, as well as physician’s global assessment of disease activity, number of active joints, remission rate, HAQ and SF-36 after 15 years, but the non-participants were slightly younger at onset than the participants (6.9±4.7 vs 8.2±4.1 years; p=0.032). After 30 years, the 86 patients who were not examined had lower levels of HAQ and higher levels of well-being and SF-36 Physical Component Score (PCS) than the 90 examined patients (all p<0.001; data not shown).

Remission and medication

After median 30 years, 73 patients (41%) had active disease (n=60) or were in remission on medication (n=13), and 103 patients (59%) were in clinical remission off medication (table 1).

Out of 61 patients with active disease at 15-year follow-up, 39 (64%) had active disease after 30 years. Out of 98 patients in remission off medication at 15 years, 85 (87%) were still in remission at 30-year follow-up. In total, 124/176 patients (70%) had an unchanged category of disease activity from 15-year to 30-year follow-up, whereas 52 patients (30%) changed category of disease activity.

During the first 15 years of disease, 123 patients (70%) had received disease-modifying antirheumatic drugs (DMARDs), including 46 patients (26%) treated with methotrexate. Out of the 73 patients who were not in remission off medication at 30 years, 41 patients (56%) used DMARDs (26 patients), biological immunosuppressants (27 patients) and/or prednisolone (six patients). Thirty-two patients (44%) used no medication or non-steroidal anti-inflammatory drugs only, but they had higher physician’s global assessment, number of active joints and reduced well-being compared with those who used DMARDs, biological medicine and/or prednisolone (all p<0.05). The patients in remission off medication had significantly lower levels of HAQ and higher levels of well-being and SF-36 PCS than those with active disease (all p<0.001, data not shown).

Nine (5%) patients reported uveitis during the last 12 months and 16% ever had uveitis.

JADAS3

Table 2 shows the remission rates and median JADAS3 values after median 30 years according to the ILAR JIA classification categories.

There was a statistically significant difference in remission rates with the highest rates in those with persistent oligoarticular and systemic JIA (80% and 83%, respectively), and the lowest in those with polyarticular rheumatoid factor (RF)-positive JIA (17%) and enthesitis-related arthritis (ERA; 37%, p=0.001). The JADAS3 was median 1.9 (range 0.2–23.1) for the total

Table 1 Changes in disease activity categories from 15-year to 30-year follow-up in patients with juvenile idiopathic arthritis (JIA)

<table>
<thead>
<tr>
<th>Disease activity at 15-year follow-up*</th>
<th>Disease activity at 30-year follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease</td>
<td>Remission on medication</td>
</tr>
<tr>
<td>Active disease</td>
<td>61 (35)</td>
</tr>
<tr>
<td>Remission on medication</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Remission off medication</td>
<td>98 (56)</td>
</tr>
<tr>
<td>Total</td>
<td>176 (100)</td>
</tr>
</tbody>
</table>

Values refer to the number of subjects (%).

*According to preliminary criteria for clinical remission in JIA.5
study group. There were differences in the JADAS3 across JIA categories (p = 0.019). Patients with systemic JIA or persistent oligoarthritis had lower levels of JADAS3 than those with polyarticular RF-positive JIA (all p < 0.01).

The JADAS3 was median 6.0 (range 1.1–23.1) for patients with active disease, 2.2 (range 0.2–11.7) for patients in remission on medication and 0.5 (range 0.2–7.7) for patients in remission off medication (p < 0.001) at 30 years. Seventy-two (41%) of the 176 patients had JADAS3 >4.5, 80% had active disease and 20% were in remission (16% >4.5, 80% had active disease, remission on/off medication, Spearman’s correlation coefficient 0.73 (p < 0.001).

Table 2 Remission rates and distribution of the JADAS3 at 30-year follow-up according to the ILAR classification of JIA

<table>
<thead>
<tr>
<th>ILAR classification</th>
<th>In remission off medication*</th>
<th>JADAS3†</th>
<th>JADAS3 0–1.0</th>
<th>JADAS3 1.1–2.0</th>
<th>JADAS3 2.1–4.5</th>
<th>JADAS3 &gt;4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arthritis</td>
<td>12 (7)</td>
<td>0.6 (0.4 to 5.1)</td>
<td>8 (67)</td>
<td>2 (17)</td>
<td>1 (8)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Polyarticular RF negative</td>
<td>25 (14)</td>
<td>3.9 (0.4 to 10.5)</td>
<td>7 (28)</td>
<td>2 (8)</td>
<td>5 (20)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Polyarticular RF positive</td>
<td>6 (3)</td>
<td>4.5 (1.4 to 23.1)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>2 (33)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Oligoarticular persistent</td>
<td>50 (28)</td>
<td>0.8 (0.2 to 12.7)</td>
<td>26 (52)</td>
<td>7 (14)</td>
<td>9 (18)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Oligoarticular extended</td>
<td>24 (14)</td>
<td>2.6 (0.4 to 13.3)</td>
<td>8 (33)</td>
<td>4 (17)</td>
<td>5 (21)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td>27 (15)</td>
<td>3.1 (0.2 to 15.6)</td>
<td>10 (37)</td>
<td>3 (11)</td>
<td>4 (15)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>21 (12)</td>
<td>2.8 (0.3 to 12.1)</td>
<td>7 (33)</td>
<td>3 (14)</td>
<td>3 (14)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
<td>11 (6)</td>
<td>0.7 (0.4 to 11.7)</td>
<td>6 (55)</td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Total</td>
<td>176 (100)</td>
<td>1.9 (0.2 to 23.1)</td>
<td>72 (41)</td>
<td>23 (13)</td>
<td>31 (18)</td>
<td>50 (28)</td>
</tr>
</tbody>
</table>

Values refer to numbers (%) or median (range).

*p = 0.001 for differences between categories.

†p = 0.019 for differences between categories.

JADAS3, Juvenile Arthritis Disease Activity Score, clinical version; RF, rheumatoid factor; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis.

Predictors of active disease

Predictors of active disease were analysed by multiple logistical regression analyses. All the core set variables at 15 years were associated with active disease at 30-year follow-up. Predictors of ‘active disease or being in remission on medication’ at 30 years were: HLA-DRB1*01 (DR1) positivity (OR 8.5, 95% CI 2.6 to 28.1), physician’s global assessment of disease activity at 15-year follow-up (OR 5.7, 95% CI 2.7 to 12.2) and a short duration of total time in remission at 15 years (OR 7.9, 95% CI 2.8 to 22.6) (table 3).

The same variables were identified when the dependent variable was exchanged with ‘having active disease’ (not being in remission on/off medication, data not shown), except that CRP at 15 years came out as an additional predictor (OR 3.2, 95% CI 1.3 to 7.9).

Physician’s global assessment of disease activity at 15 years was a predictor of a high symptom state (JADAS3 >4.5) at 30-year follow-up (OR 2.4, 95% CI 1.7 to 3.5).

Comparing health status at 15-year and 30-year follow-up

After 30 years, 79 (45%) of the 176 patients had a HAQ disability index >0. We compared health status and disease activity at 15 years with that of 30-year follow-up in 90 patients who had active disease or needed medication at 15 years or later (table 4). There were significant improvements in physician’s global assessment of disease activity, number of active joints, ESR and CRP (all p < 0.05), but not in number of joints with LROM, patient’s global assessment, HAQ and SF 36 (table 4).

DISCUSSION

The present study shows that 41% of the patients with JIA were not in remission off medication after 30 years of disease duration, 46% had a JADAS3 >2 and 28% had a high symptom state. The overall remission rates at 15 years were comparable with rates at 30 years, physician’s assessment of disease activity and inflammatory markers were improved, but patient-reported health status was not. DR1, elevated CRP, high physician’s global assessment of disease activity and a short duration in remission at 15 years predicted disease activity at 30-year follow-up.

The finding that 41% of the patients had persistently active disease or were on antirheumatic medication after 30 years is in accordance with several long-term studies which have reported active disease in 37%–43% of patients after 21–28 years of disease duration. However, Peterson et al found self-reported...
in studies with lower remission rates. After 30 years, only 56% of the 73 patients with active disease were on DMARDs, prednisolone and/or anti-tumour necrosis factor treatment, suggesting that a considerable part of the patients were not satisfactorily treated. Our results support that JIA is not a self-limiting disease for a substantial proportion of the patients.

The remission rates for the categories of JIA showed the same trend as in studies with shorter follow-up. Most patients with persistent oligoarticular JIA were in remission (80%), in contrast to patients with polyarticular RF-positive JIA where only one patient was in remission. Interestingly, 83% of the 12 patients with systemic JIA were in remission. In Scandinavia this patient group is small, and other studies have reported similar remission rates (75%-83%) in systemic JIA.

The overall disease course seemed to be stable in 70% of the patients between 15-year and 30-year follow-up. Eighty-seven per cent of the patients in remission off medication were in the same category at 30 years, and the disease remained active in 64% of those with active disease at 15 years. This is in contrast to a recent study where only 61% of the patients with juvenile chronic arthritis who were in remission at 5-year follow-up were in remission at 17-year follow-up. Studies of patients with JIA with disease duration <10 years have reported cyclic episodes of remission and active disease, and Wallace et al found that patients with other JIA categories than

### Table 3 Predictors of persistent disease activity and a high symptom state at 30-year follow-up

<table>
<thead>
<tr>
<th>Dependent and independent variables</th>
<th>Univariate analyses†</th>
<th>Multivariate analyses†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Active disease or on medication at 30 years†</td>
<td>0.4 (0.2 to 0.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Oligoarticular onset§</td>
<td>0.3 (0.2 to 0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Polyarticular course¶</td>
<td>3.5 (1.7 to 7.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>PGA at 15 years</td>
<td>2.4 (1.7 to 3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Having active joints at 15 years</td>
<td>7.8 (1.9 to 7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Having joints with LROM at 15 years</td>
<td>4.5 (2.9 to 7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR &gt;15 mm/h at 15 years</td>
<td>2.4 (1.1 to 5.0)</td>
<td>0.024</td>
</tr>
<tr>
<td>CRP &gt;5 mg/L at 15 years</td>
<td>3.3 (1.7 to 6.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patient’s global ≥3 at 15 years</td>
<td>5.4 (2.4 to 12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAQ &gt;0 at 15 years</td>
<td>5.4 (2.4 to 12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total time in remission &lt;8 years at 15-year follow-up</td>
<td>14.7 (6.6 to 32.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 4 Longitudinal data on health status in 90 patients with JIA with signs of active disease after at least 15 years of disease duration

<table>
<thead>
<tr>
<th>Variables</th>
<th>15 years</th>
<th>23 years</th>
<th>30 years</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician’s global, Likert</td>
<td>2.3 (1.1)</td>
<td>na</td>
<td>1.8 (0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of active joints</td>
<td>3.0 (5.4)</td>
<td>na</td>
<td>1.5 (2.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>No. of joints LROM</td>
<td>6.3 (8.8)</td>
<td>na</td>
<td>7.8 (11.7)</td>
<td>0.104</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>14.3 (15.5)</td>
<td>na</td>
<td>10.8 (11.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>9.7 (13.7)</td>
<td>na</td>
<td>4.2 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient’s global, Likert</td>
<td>2.7 (0.9)</td>
<td>2.8 (1.0)</td>
<td>2.9 (0.9)</td>
<td>0.359</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.4 (0.5)</td>
<td>0.4 (0.5)</td>
<td>0.5 (0.5)</td>
<td>0.184</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>45.2 (10.3)</td>
<td>45.3 (10.1)</td>
<td>44.5 (9.9)</td>
<td>0.580</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>51.9 (8.6)</td>
<td>49.8 (10.9)</td>
<td>50.5 (10.1)</td>
<td>0.291</td>
</tr>
</tbody>
</table>

Numbers are mean values (SD).
persistent oligoarthritis spent minimum two-thirds of their disease course in a state of active disease. We did few examinations during the disease course, and some variation of disease activity and medication may have been lost. Our results suggest that although the disease activity may vary considerably during the first years, it seems to get more stable in adults with JIA.

In the 90 patients with signs of active disease after at least 15 years, physician reported data on disease activity improved over time, but patient-reported health status did not. In addition to disease activity, patient’s global assessment, HAQ and SF-36 may incorporate overall well-being, disability, damage and psychosocial effects of the disease. There are a limited number of studies of more than 20 years of follow-up in patients with JIA, and only one of them used repeated evaluations of the patients. The fact that disability did not increase significantly over time is in contrast to older studies. However, these studies were performed three to five decades ago and factors like new treatment modalities may have influenced our results.

We found that physician’s global assessment of disease activity at 15 years predicted disease activity at 30 years, also when measured as a JADAS3 >4.5. CRP and less time in remission during the first 15 years also predicted active disease. Few studies have looked for predictors of more than 20 years outcome. In a Swedish study remission at 5-year follow-up predicted remission at 17-year follow-up. Magnani et al. found that patients with JIA who had one or more episodes of inactive disease during the first 5 years had better outcomes at 7-year follow-up than those who had continuous disease activity. Flato et al. found that persistently elevated ESR the first 6 months of the disease predicted active disease at 15-year follow-up in the present patient cohort.

DRI1 was also a predictor of persistent disease activity. DRI1 has previously been associated with a polyarticular course in patients with oligoarticular onset and with RF-positive polyarticular JIA.

JADAS is a relatively new instrument for patients with JIA. Several studies on patients with short disease duration have used it. The JADAS has been evaluated for children with JIA. We have used JADAS in adult patients. One previous study applied JADAS in adults. We found that JADAS3 correlated strongly with categories of disease activity in our adult patients, but experienced that JADAS3 additionally may capture other aspects of the burden of disease like damage and overall well-being, as some patients in remission had high symptom states (JADAS3 >4.5).

The study has some limitations. We chose to use the JADAS3 version, even though the cut-off values for acceptable symptom state were defined according to JADAS. In those patients who had elevated ESR, a JADAS score would have been slightly higher than a JADAS3 score, and thus our results should be interpreted with this in mind. Patients in remission off medication after 15 years were clinically re-examined only if they reported signs of disease activity by questionnaires after 23 or 30 years. However, the non-examined patients had significantly better health status after 30 years than those examined, supporting that their disease was in remission. Another limitation of the study is that we used the preliminary criteria for remission in patients with ERA, psoriatic arthritis and undifferentiated JIA. The criteria have not been evaluated for these categories, but other studies have nevertheless applied them to comprise their total patient groups.

The strength of this study is the long follow-up time of 30 years, with repeated assessments of clinical data and questionnaires. It is also the first long-term study that includes the remission criteria for JIA and the JADAS. Our patient cohort has previously been described with characteristics comparable with those in epidemiological studies. However, the non-participants were significantly younger at disease onset than the participants. This is probably of minor importance for the results, as the disease activity in these two groups was not significantly different at 15 years. Since the 15-year follow-up, six patients had died. We have not examined their cause of death, this will be the focus of future work, but none of the six patients had systemic JIA. It is possible that severe disease could have influenced their deaths, thus eliminating some patients with active disease from this follow-up.

In this long-term study we have reported that the overall remission rates were similar at 15-year and 30-year follow-up. After 30 years, 41% of the patients were not in remission off medication and 28% had a high symptom state. Physician’s assessment of disease activity and inflammatory markers improved over the years, but patient-reported disability and health status did not. Treatment and rehabilitation of patients with JIA have improved during the last decades. More long-term studies into adulthood are needed to reveal the consequences of the present treatment regimes.

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**REFERENCES**


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