Changing patterns in treatment, remission status and categories in a long-term Nordic cohort study of juvenile idiopathic arthritis

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Abstract

Objective: To explore sustainability of achieved remission off medication and defined ILAR categories in juvenile idiopathic arthritis (JIA). To describe the trajectory of disease course over time by comparing treatment, disease activity and ILAR categories from baseline, 8 and 18 years of disease.

Methods: Included were 373 of the 510 initially recruited consecutive cases of JIA from the prospective longitudinal, population-based Nordic JIA cohort with disease onset during 1997-2000 from Denmark, Norway, Sweden, and Finland in an 18-year follow-up study. Clinical data was collected consecutively at baseline, 8 and 18 years of disease, and evaluated regarding treatment, disease activity and ILAR category.

Results: Significantly more patients (70%) were off medication after 18 years of follow-up compared to after 8 years (59.7%); nevertheless, the number of patients in remission had not increased (52% versus 51%). Twelve percent of patients changed ILAR category between 8 and 18 years after disease onset. Almost half of the changes were due to updated information about heredity in a first degree relative. In the same period, the psoriatic group increased significantly in number ($p<0.001$) contrasting the oligoarticular category, which decreased ($p=0.02$). The undifferentiated group increased 24% from 8 to 18 years, however, this was not significant ($p=0.06$).

Conclusion: In this Nordic JIA cohort study the remission rate did not increase even though significantly more patients were off medication at the 18-year follow-up compared to 8 years after disease onset. The distribution of patients in the ILAR categories continued to change significantly throughout the 18-year study period.

Keywords: Juvenile idiopathic arthritis, ILAR classification, remission, long-term outcome.

Significance and Innovations

- We found significantly more patients off medication 18 years after disease onset compared to the 8-year follow-up, but the number of patients in remission off medication had not increased correspondingly.

- The distribution of patients within the ILAR categories defined from baseline were not sustained, but changed significantly even beyond 8 years after disease onset.

- Almost half of the changes in the distribution between the ILAR categories were caused by updated information on heredity in a first degree relative obtained at the follow-up visits.

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic immune-mediated inflammatory disease in childhood with a miscellaneous disease spectrum from monophasic to chronic, often fluctuating and unpredictable disease course. The variability of outcome and complications warrant grouping into homogeneous categories according to distinct phenotypes, pathophysiology, biochemical findings, disease course and prognosis. Distinguishing the different classification criteria is essential for clinical trials and epidemiologic studies such as long-term outcome investigations. According to the International League of Associations for Rheumatology (ILAR) consensus-based classification criteria, there are seven exclusive JIA categories: 1) systemic arthritis (sJIA); 2) oligoarthritis (persistent and extended); 3) polyarticular rheumatoid factor (RF) negative; 4) polyarticular RF positive; 5) psoriatic arthritis (JPsA); 6) enthesitis-related arthritis (ERA); 7) undifferentiated arthritis (1). Undifferentiated JIA is applied if criteria for other categories are neither met nor allow unambiguous classification. The ILAR criteria proposed in 1995 (2) were revised in 1998 (3) and in 2004 (1) to correct misconceptions. However, ongoing criticism about the current criteria has been raised and contrary to the intentions of the ILAR criteria, the distribution of patients for most categories tends to change over time in the first decade of the disease course (4).

Current treatment recommendations propose the use of medication tailored according to clinical manifestations as previously described (5-10). The scale of research in this field is still advancing and modern therapies have evolved the outcomes of JIA due to the increasing variety of targeted therapies that are available (11, 12). Etanercept was the first biologic drug studied in polyarticular JIA and the randomized controlled trial (RCT) was published in 2000 (13). In the following two decades several RCT studies on anti-tumor necrosis factor (TNF) agents, CD28 receptor antagonist, IL-1 inhibitors, and anti-IL-6 receptor antagonist have been published in JIA (14-16). Despite the revolutionary leap in treatment options, we found that JIA continues to be an ongoing chronic disease with only 33% in clinical remission off medication (CR) even 18 years after disease onset (17). Furthermore, we have shown that the ILAR categories defined at disease onset change considerably during the first 8 years of disease course (4).

In the past two decades two other studies have reported longitudinal data on long-term outcome with a follow-up of more than 10 years (18, 19) but both the 15- and 17-year follow-up in these

studies are from the prebiologic era before year 2000. No previous study has reported on the longitudinal changes in ILAR criteria beyond 8 years after disease onset. Yet, there is a shortage of conclusive data about the sustainability of the defined ILAR categories, medical treatment and achieved remission beyond the first decade of disease and this has been addressed in the present study. We aimed to investigate the longitudinal trajectory of JIA disease course over time by comparing ILAR categories, treatment and disease activity from baseline, 8 and 18 years of disease.

Patients and Methods

Study design:

We performed a multi-center, prospective population-based cohort study from the Nordic JIA cohort with baseline, 8-year and 18-year follow-up. Included were all consecutively, newly diagnosed patients from defined geographical areas of Denmark, Norway, Sweden and Finland with onset of JIA between January 1st, 1997 and June 30th, 2000. JIA was classified according to the International League of Associations for Rheumatology (ILAR) criteria (1). Totally, 510 participants were included in the cohort.

For the three follow-up visits, all previously included participants were invited regardless of disease status. Data from baseline, 8-year and 18-year follow-up have previously been published individually (4, 17, 20).

Inclusion criteria: All eligible participants fulfilling the ILAR criteria (1) who had at least 3 study visits at baseline, 8 and 18 years after onset. *Exclusion criteria*: None.

Data collection:

Demographics, treatment, disease characteristics and blood samples were collected at the study visits. Additionally, a clinical examination was performed. We offered a standardized telephone interview to those who could not attend a study visit and a crosscheck of the validity of the information was performed in the medical records.

Treatment: Medications were categorized as non-steroidal anti-inflammatory drugs (NSAIDs), systemic steroids taken at the time of the follow-up visit, conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs) and biologic drugs, bDMARDs. cDMARDs included methotrexate, azathioprine, hydroxychloroquine, leflunomide, sulfasalazine and mycophenolate mofetil. The bDMARDs used included etanercept, infliximab, adalimumab, certolizumab, golimumab, rituximab, abatacept, anakinra and tocilizumab. DMARDs refers to the use of cDMARDs and/or bDMARDs.

Inactive disease and remission: We applied the preliminary Wallace criteria (21) for clinical inactive disease (CID), which embraces: 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 physician's global assessment of the disease activity (PhysGA) with best score attainable indicating no disease activity. For clinical remission on medication (CRM), the criteria for inactive disease on systemic anti-inflammatory medication had to be fulfilled for a minimum of 6 continuous months. For clinical remission off medication (CR) the patients must have had inactive disease for a continuous period of at least 12 months off all anti-arthritis and anti-uveitis medication (21).

An active joint was defined as a joint with swelling and/or a joint with limitation on motion accompanied by pain and/or tenderness. We defined a normal ESR as a value below 20 mm per first hour, and a normal CRP level as below 10 mg/L. PhysGA was assessed by a visual analogue scale (VAS).

Statistical analysis: Descriptive statistic was used to describe demographics and clinical characteristics. Pearson´s chi-squared test was used to analyze odd ratios in categorical, unmatched data. Fisher´s exact test was used to analyze risk ratios between groups for categorical variables and Mann-Whitney U test to compare medians for continuous variables. For the within-person analysis shown in Table 4, we used the case-control odds ratio calculator in STATA.

Ethical approval: Approval from medical ethics committees and data protection authorities were obtained. Written informed consent from all participants was achieved according to the regulations of each participating country.

Results

Of 510 eligible participants, 422 (82.7%) attended the 18-year follow-up. In total, 373 completed at least three follow-ups (Figure 1); at median 7 months, 8.1 years and 17.6 years after disease onset (Table 1). At the time of inclusion all participants attended a clinical visit, and at the 8- and 18-year follow-up the numbers were 357 of 450 (79.3%) and 319 of 422 (75.6%), respectively, while the rest participated through a telephone interview (Figure 1). In total, 291 of 373 (78.0%) attended a clinical visit at all three time points.

The demographic data of the cohort is presented in Table 1. Comparison of the participants and those lost to follow-up revealed no significant difference in baseline characteristics (Table 2).

Changes in therapeutic drug use: Out of the 373 participants with a follow-up at all three time-points, the proportion of children not receiving DMARDs at baseline were 273/373 (73.2%). At the 8-year follow-up, 59.7% did not receive DMARDs, and at the 18-year follow-up this proportion increased significantly to 70.0% (risk ratio (RR) 1.3, p=0.003) (data not shown).

Out of the 103 participants treated with cDMARDs (either as monotherapy or in combination with bDMARDs) at the 8-year follow-up, 44 (42.7%) were still using cDMARDs at the 18-year follow-up (RR 0.4, p<0.001) (data not shown). Additionally, out of the 52 participants treated with bDMARDs (either as monotherapy or combined with cDMARDs) at the 8-year follow-up, 32 (61.5%) were still receiving bDMARDs at the 18-year follow-up (RR 0.6, p=0.02).

Few participants used non-steroidal anti-inflammatory drug (NSAID) as monotherapy (3 versus 2 at the 8- and 18-year follow-up visit, respectively).

Among the 373 participants, 55 participants (14.7%) did not receive any treatment for JIA during the entire period from the 8-year to the 18-year follow-up and conversely, 85 of the 373 (22.8%) were on continuous, DMARDs treatment due to either uveitis or arthritis during the same period. In total, 33 out of the 85 (38.8%) were diagnosed with uveitis at some point of the disease course.

At some point during the disease course, 76.9% of the participants with sJIA were treated with DMARDs. For the other categories the corresponding numbers were 27.6% (oligoarticular persistent), 77.3% (oligoarticular extended), 89.7% (polyarticular RF negative), 66.7% (polyarticular RF positive), 65.2% (JPsA), 75.7% (ERA), 58.9% (undifferentiated) and 62.7% for the total cohort.

In total, 287/373 (76.9%) had joint injections performed in median 3 joints (IQR 0-8.5) at some time point between baseline and the 8-year follow-up. Between the 8- and the 18-year follow-up the number was 146/373 (39.1%), also with a median of 3 joints (IQR 2-7).

Among those who did not receive any medication irrespective of the JIA categories, we grouped the participants off medication at the 18-year follow-up in oligo- (≤ 4 cumulative joints) and polyarticular course (>4 cumulative joints). Among participants with an oligoarticular course 123/136 (90.4%) were off medication at the 8-year follow-up and 132/237 (55.7%) with a polyarticular course were off medication. At the 18-year follow-up 120/136 (88.2%) were off medication in the oligoarticular group and 148/237 (62.4%) with a polyarticular course were off medication.

Of the 139 participants that never received any DMARDs during their disease course, 85.5% received one or more intraarticular corticosteroid injections and the remaining participants received NSAIDs alone.

Autologous bone marrow transplantation was performed in one participant with recalcitrant sJIA. Allogeneic transplantation was completed in one participant with ERA due to aplastic anemia during a period of clinical remission of his JIA.

Changes in disease status: The median number of active and cumulative joints at baseline was 3 (range 1-30). At the 8-year visit the median number of active joints were 0 (range 0-13) and the number of cumulative joints affected were 6 (range 1-41). Similarly, the numbers at the 18-year follow-up were median 0 (range 0-5) and 7 (range 1-47), respectively.

Out of 151 who were in remission off medication 8 years after disease onset, 32% did not remain so. Median duration of remission off medication at the 18-year follow-up was 11.5 years (IQR 6.3-15.5 years) (data not shown).

Overall, 147 participants had missing data regarding remission status on at least one of the follow-up visits. To estimate the likely impact of these participants on the results we made an assumption that all missing patients either were in 'remission off medication' or 'not in remission' at the 8- and 18-year follow-up. If all participants lost to follow-up were in remission off medication, 298/510 (58% (CI 54-63%)) and 302/510 (59% (CI 55-63%) would be in remission off medication at the 8-year follow-up and at the 18-year follow-up, respectively. Conversely, if all participants lost

to follow-up were not in remission the corresponding numbers would be 30% (CI 26-34%) and 30% (CI 27-35%).

Among the 34 participants in remission on medication 8 years after disease onset, the majority (18/34 (53%)) were in remission on or off medication at the last follow-up (RR 0.5, p<0.02).

Changes in ILAR category: Distribution of patients amongst the ILAR categories continued to change throughout the study period of 18 years (Figure 4).

Altogether, 289/422 (68.5%) participants were categorized into the same ILAR category throughout the study period. From baseline to 8-year follow-up 30 patients (7%) changed ILAR category; furthermore, 46 (11%) changed category between 8- and 18-year follow-up.

During the study period, there was a significant decrease in the combined persistent and extended oligoarticular categories and a significant increase in the psoriatic arthritis group (Table 4).

Of the 230 participants with oligoarticular disease at baseline, 84 (36.5%) developed an extended course at 18-year follow-up (Table 4).

Almost half of the shifts between ILAR categories (30/63; 47.6%) were due to updated information on ankylosing spondylitis, psoriasis or acute anterior uveitis in a first degree relative.

In the psoriatic arthritis group, 22 participants were added from other ILAR categories during the disease course, of which 18 (81.8%) developed psoriasis. In 4 cases the reasons were a first degree relative with psoriasis combined with one of the following findings; nail pitting, onycholysis or dactylitis. Two patients left the psoriatic category because of new information of a first degree relative with ankylosing spondylitis.

Among 29 participants that changed to the undifferentiated group during the disease course, 25 (86.2%) were added because of new information on first degree relative with psoriasis or ankylosing spondylitis. In one case RF positivity developed (two tests >3 months apart), two participants fulfilled both ERA and JPsA categories, and one male case who later developed psoriasis was excluded from the JPsA group because he was HLA-B27 positive with disease onset after his 6th birthday.

The ERA category also increased during 18-year follow-up. Additional 12 participants fulfilled the criteria for this category during disease course due to enthesitis (5), sacroiliitis (4), first degree relative with ankylosing spondylitis (2) or acute anterior uveitis (1), and two participants left the

category (one fulfilled two categories and one was a boy with disease onset at 7.2 years, HLA-B27 positive who later developed psoriasis).

Discussion

In this 18-year prospective study in a population-based setting we found a no further improvement of the remission rate from 8 years of disease and frequent change of ILAR categories during the disease course. Significantly more patients were off medication after 18 years of follow-up (70%) compared to 8 years after onset (60%), but the number of patients in remission off medication did not increase (52% versus 51%). Distribution of patients amongst the ILAR categories as defined after 8 years was not sustained but changed significantly by 11% during the period from 8 to 18 years. The oligoarticular category decreased significantly, the psoriatic group increased significantly, and there was an increasing trend for the undifferentiated group. In almost half of the cases (47.6%) the change was due to heredity of ankylosing spondylitis, psoriasis or acute anterior uveitis in a first degree relative.

Few studies have investigated longitudinal drug use in JIA with a follow-up of more than 15 years. The new treatment options have changed dramatically since the introduction of biologics and not surprisingly, we found an increase in the use of biologics during the observation period of 18 years. Furthermore, we found an increased risk ratio of being off any systemic treatment 18 years after disease onset of 1.3 if you were off medication at the 8-year follow-up. Almost 60% were off all medication after 8 years which increased to 70% after 18 years. For comparison, in a single center study from Norway, Selvaag et al (18) reported that 56% of their cohort (n=176) used no systemic treatment at the 15-year follow-up which increased to 87% after 30 years of disease duration. In contrast, a Swedish population-based cohort-study by Bertilssson et al (19) found that 85% were off cDMARDs after 5 years (n=129 patients) which decreased to 75% at the 17-year follow-up (n=86). Even though these two cohorts were collected almost two decades before our cohort (1980-85) and the treatment strategies have changed noticeably since then, the rates of patients off systemic treatment were comparable to what we found (70% after 18 years). This might indicate that the drug used improve the sequelae of the disease but not the disease course by its very nature. A recent retrospective, 6-year follow-up study on 247 patients from two

Canadian centers described that 47% were in remission off medication and 25% were in remission on medication at the last follow-up(22) which is in line with our findings.

Despite increased chance of being off medication at 8 and 18-years of disease, the remission rate did not increase similarly. Given the counterintuitive finding that remission rate is stable, but withdrawal of medication is increased one can speculate that some participants neglect mild disease activity by not taking the medication and for the same reason maybe they do not want affiliation with an outpatient clinic and regular follow-up visits (17). In two cases the disease activity was because of unknown uveitis activity found due to participation in the study. We have previously described that 19% of the participants in this cohort have morning stiffness more than 15 minutes as the only sign of disease activity. In 68.5% of cases there was stability throughout the disease course from 8 to 18-years after disease onset. Of the 151 patients being in remission off medication after 8 years of disease, 69% were still in remission after 18 years. Similarly, Selvaag et al found that altogether, 70% had a stable disease course between 15 and 30 years of follow-up (18), and of those in remission off medication after 15 years 87% remained in that category. In contrast, Bertilsson et al (19) described a stable remission course in 61% between years 5 to 17 of the disease; however, they applied their own definition of remission as no evidence of active synovitis and/or active extraarticular features and without drugs for ≥ 2 years, hampering comparison. Our results suggest that despite some continued individual shifts between active disease and remission in more than 30%, the overall disease status of the cohort remains unchanged for the majority between 8 and 18 years. That means that if you are in remission off medication 8 years after disease onset this is likely to persist for the following 10 years. Likewise, if you are not in remission after 8 years you are more prone to remain so.

Using the ILAR criteria for JIA have been an object of fierce criticism over time (2, 23-27) and although the revisions addressed some weaknesses, several challenges endure (2, 28). Beyond many concerns about simplification and lack of validation in large cohorts there remain inclusion criteria not assessed in clinical practice and exceedingly restrictive exclusion criteria that for some categories appear to be too rigid. Furthermore, inclusion/exclusion criteria may induce changes in the distribution of patients amongst the ILAR categories over time due to supplementary information regarding heredity or development of new onset rheumatic diseases among first

degree relatives (4). Evidently, it can be difficult to obtain a reliable history of HLA-B27 associated disease or psoriasis among relatives (28) and recorded family history may not be applied repeatedly and strictly enough to keep it continuously updated, leading to an inappropriate, unadjusted classification.

Altogether, this strains the credibility of the ILAR classification over time. We found that information about heredity continued to change over time in our cohort; hence, the exclusion criteria accounted for almost half of the changes in ILAR category. In our study, 32.8% changed ILAR category during the observation period and in comparison, Bertilsson et al (19) observed that 44% changed category during their follow-up of 17 years. Nevertheless, they used the European Alliance of Associations for Rheumatology (EULAR) criteria for categorizing juvenile chronic arthritis which hamper comparability.

The psoriatic group increased significantly over time, but 2 participants left the category because of ankylosing spondylitis diagnosed in a first-degree relative. Although not significant, the group of undifferentiated JIA increased over time mainly because of development of psoriasis or ankylosing spondylitis in a first degree relative which is in line with other studies (29-31). Originally, the undifferentiated category was merely intended to be a temporary group that would conceivably decrease over time (24, 26, 28); however, this was not confirmed in our study and this category by virtue of its lack of homogeneity is most unlikely to be suitable for research. Our findings support the idea to withdraw or at least modify the exclusion criteria in the new data-driven classification criteria proposed by the Pediatric Rheumatology International Trial Organization (PRINTO) (26) to ensure more pristine and homogeneous entities.

Several strengths of this study have to be emphasized. To our knowledge this is the only long-term, multicenter, population-based cohort study including ongoing disease activity with a follow-up of more than 15 years using the ILAR classification of JIA. The proportion of lost-to-follow-up is acceptable with reliable data on 83.7% of the cohort. The use of validated definitions on disease activity and ILAR classification facilitate comparison with other studies.

A limitation is that the inclusion period is at the very dawn of introduction of biologic medicines and this might impede comparison with outcome studies of today. The small sample size in some categories limit the conclusions to be drawn. Additionally, 137 participants did not attend one or

more follow-up visits and this might bias the results. The distribution of the ILAR categories among the missing and the included participants were similar except for the polyarticular RF+ category; however, caution must be applied when interpreting the changes in ILAR category over time due to missing data. Regarding remission off medication, we calculated the sensitivity of the worst and the best scenario. One could speculate that the participants with a disease no longer playing a prominent part of their daily lives are more prone not to attend a follow-up, which may skew the outcomes in a more severe direction.

In summary, in this population-based setting significantly more patients were off medication at 18-year follow-up compared to 8 years after disease onset; however, the number of patients in remission off medication had not increased. The ILAR categories as defined at baseline were not sustained but changed significantly even beyond 8 years after onset.

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Table 1. Characteristics of the Nordic JIA cohort of participants with a follow-up at baseline, 8-year and 18-year and participants with a follow-up at all three time points (baseline, 8- and 18 years).

	Baseline (n=510)	8-year follow-up (n=450)	18-year follow-up (n=422)	Follow-up at 3 time points (n=373)
Females, n (%)	340/510 (66.7)	299/450 (66.4)	288/422 (68.2)	249/373 (66.8)
Age at onset, years	5.9 (2.8-10.0)	5.5 (2.5-9.7)	5.7 (2.6-9.7)	5.5 (2.3-9.4)
Age at follow-up, years	6.6 (3.3-10.8)	14.2 (10.6-17.6)	23.4 (20.3-27.3)	23.3 (20.2-27.3)
Follow-up time, years	0.6 (0.5-0.7)	8.2 (7.9-8.5)	17.6 (16.8-18.4)	17.6 (16.8-18.4)
ANA positive, n (%)	154/442 (34.8)	148/434 (34.1)	141/383 (36.8)	133/365 (36.4)
HLA-B27 positive, n (%)	104/481 (21.6)	94/433 (21.7)	87/406 (21.4)	79/363 (21.8)
JIA categories, n (%)				
Systemic JIA	18 (3.5)	17 (3.8)	14 (3.3)	13 (3.5)
Persistent oligoarthritis	275 (53.9)*	139 (30.9)	113 (26.7)	98 (26.2)
Extended oligoarthritis	-	80 (17.8)	84 (19.9)	78 (20.9)
Polyarticular RF-negative	108 (21.1)	81 (18.0)	73 (17.3)	68 (18.2)
Polyarticular RF-positive	10 (2.0)	4 (0.9)	6 (1.4)	3 (0.8)
Psoriatic arthritis	9 (2.0)	14 (3.1)	28 (6.6)	23 (6.1)
ERA	38 (7.5)	47 (10.4)	41 (9.7)	37 (9.9)
Undifferentiated arthritis	52 (10.2)	68 (15.1)	63 (14.9)	56 (15.0)
Treatment				
No systemic treatment	402 (78.8)	289 (64.2)	268 (63.5)	-
NSAID**	262 (51.3)	51 (11.3)	79 (18.7)	-
Monotherapy NSAID	187 (36.7)	3 (0.7)	2 (0.5)	-
Systemic corticosteroids	27 (5.3)	5 (1.1)	4 (0.9)	-
Monotherapy cDMARDs	71 (13.9)	66 (14.7)	35 (8.3)	-
Monotherapy bDMARDs	0 (0.0)	15 (3.3)	37 (8.8)	-
cDMARD and bDMARDs	6 (1.2)	37 (8.2)	38 (9.0)	-

Values are presented in number (%) or median (interquartile range). JIA=juvenile idiopathic arthritis, ANA= antinuclear antibody, HLA-B27= human leucocyte antigen B27, RF= rheumatoid factor, ERA= Enthesitis-related arthritis. *Oligo articular, not yet differentiated as persistent and extended. **Non-steroidal anti-inflammatory drug

Table 2. Baseline characteristics of the 373 participants with a visit at baseline, 8- and 18 years of follow-up compared to the 137 lost to follow-up.

	Lost to follow-up (n=137)	**Follow-up at 3 time points (n=373)**	**Odds ratio (95% CI) P-value**
Females, n (%)	91 (66.4)	249 (66.8)	1.0 (0.6-1.5); p=0.94
Age at onset, years	7.1 (3.0-11.2)	5.5 (2.3-9.4)	p=0.10*
ANA positive, n (%)	21/77 (27.2)	133/365 (36.4)	0.7 (0.4-1.2); p=0.13
HLA-B27 positive, n (%)	25/118 (21.2)	79/363 (21.8)	1.0 (0.6-1.6); p=0.89
Active joint count	1 (0-3)	1 (0-3)	p=0.57*
Jadas-71	5.9 (3.4-11.0)	4.5 (1.8-11.0)	p=0.27*
JIA-category			
Systemic JIA	5 (3.6)	13 (3.5)	-
Oligoarticular	73 (53.3)	202 (54.2)	1.0 (0.6-1.5); p=0.86
Polyarticular RF-	26 (19.0)	82 (22.0)	0.8 (0.5-1.4); p=0.46
Polyarticular RF+	7 (5.1)	3 (0.0)	-
Psoriatic arthritis	3 (2.2)	6 (0.0)	-
ERA	10 (7.3)	28 (7.5)	1.0 (0.4-2.1); p= 0.94
Undifferentiated JIA	13 (9.5)	39 (10.5)	0.9 (0.4-1.8); p=0.75

Values refer to number (%) of patients or median (interquartile range). CI= confidence interval, ANA= antinuclear antibodies, HLA= human leukocytes antigen, Jadas-71= 71-joint juvenile arthritis disease activity score, JIA= juvenile idiopathic arthritis, RF= rheumatoid factor, ERA= enthesitis-related arthritis. *Mann-Whitney test

Table 3 Changes in disease status from 8-year to 18-year follow-up in participants with juvenile idiopathic arthritis, n=363*.

		DISEASE STATUS AT 18-YEAR FOLLOW-UP**		
DISEASE STATUS AT 8-YEAR FOLLOW-UP		Remission off medication	Remission on medication	Not in remission
Remission off medication	**151 (42%)**	103 (68%)	4 (3%)	44 (29%)
Remission on medication	**34 (9%)**	12 (35%)	6 (18%)	16 (47%)
Not in remission***	**178 (49%)**	40 (22%)	23 (13%)	115 (65%)
Total	**363 (100%)**	**155 (43%)**	**33 (9%)**	**175 (48%)**

Values refer to number (%) of patients. *According to the preliminary criteria described by Wallace et al. **Missing data n=10. *** Active disease or inactive disease not yet fulfilling the remission criteria either on or off medication.

Table 4. Changes in ILAR category at three time-points of follow-up in participants with JIA.

ILAR category (n=422)	Baseline	8-year FU	18-year FU	Risk ratio (95% CI); p-value*
Systemic	14	14	14	
Oligoarticular	230	218	197	0.9 (0.7-1.0); p=0.02**
- persistent		138	113	
- extended		80	84	
Polyarticular RF negative	88	81	73	0.8 (0.6-1.1); p=0.19
Polyarticular RF positive	6	6	6	
Psoriatic	8	17	28	3.5 (1.6-7.6); p<0.001**
Enthesitis-related	31	38	41	1.3 (0.8-2.1); p=0.22
Undifferentiated	45	48	63	1.4 (1.0-2.0); p=0.06

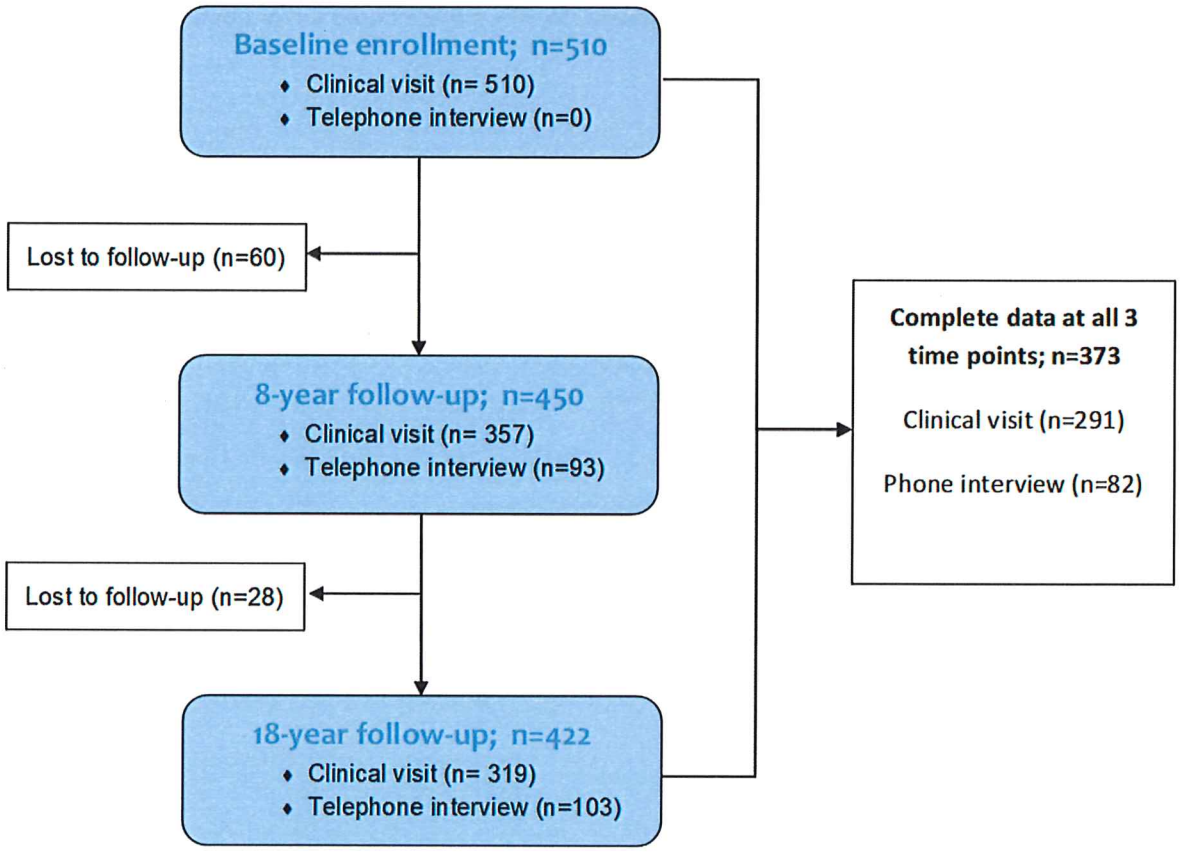
Values refer to number (%) of patients; FU=follow-up, CI=confidence interval, RF=rheumatoid factor. *Risk ratio and p-values for International League of Associations for Rheumatology (ILAR) category at baseline compared to 18-year follow-up. **Statistically significant difference between the prevalence at baseline compared to 18-year follow-up.

Figure Legends

Figure 1 Flow chart of the study population throughout the observation period of 18 years.

Figure 2 Changes in ILAR category at three timepoints of follow-up in 422 participants with JIA.
sJIA = systemic JIA, RF- = rheumatoid factor negative JIA, RF+ = rheumatoid factor positive JIA, ERA= enthesitis-related arthritis.

Figure 1


Baseline enrollment; n=510
Clinical visit (n= 510)
Telephone interview (n=0)
Lost to follow-up (n=60)
8-year follow-up; n=450
Clinical visit (n= 357)
Telephone interview (n=93)
Lost to follow-up (n=28)
18-year follow-up; n=422
Clinical visit (n= 319)
Telephone interview (n=103)
Complete data at all 3 time points; n=373
Clinical visit (n=291)
Phone interview (n=82)

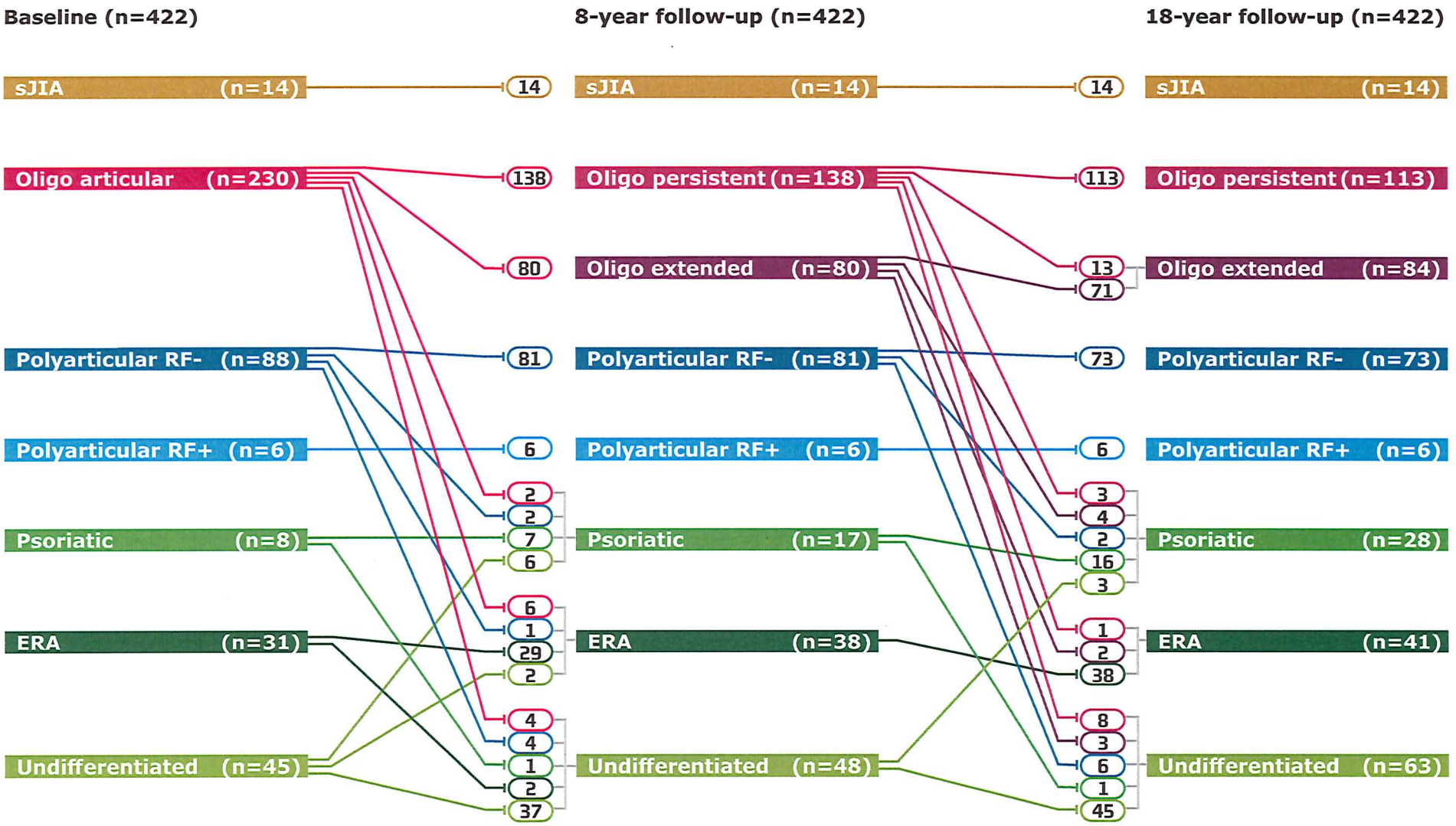

Baseline (n=422)
8-year follow-up (n=422)
18-year follow-up (n=422)
sJIA (n=14)
Oligo articular (n=230)
Polyarticular RF- (n=88)
Polyarticular RF+ (n=6)
Psoriatic (n=8)
ERA (n=31)
Undifferentiated (n=45)
14
138
80
81
6
2
2
7
6
6
1
29
2
4
4
1
2
37
sJIA (n=14)
Oligo persistent (n=138)
Oligo extended (n=80)
Polyarticular RF- (n=81)
Polyarticular RF+ (n=6)
Psoriatic (n=17)
ERA (n=38)
Undifferentiated (n=48)
14
113
13
71
73
6
3
4
2
16
3
1
2
38
8
3
6
1
45
sJIA (n=14)
Oligo persistent (n=113)
Oligo extended (n=84)
Polyarticular RF- (n=73)
Polyarticular RF+ (n=6)
Psoriatic (n=28)
ERA (n=41)
Undifferentiated (n=63)

Figure 2