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Genetics in juvenile idiopathic arthritis

Albers, H.M.

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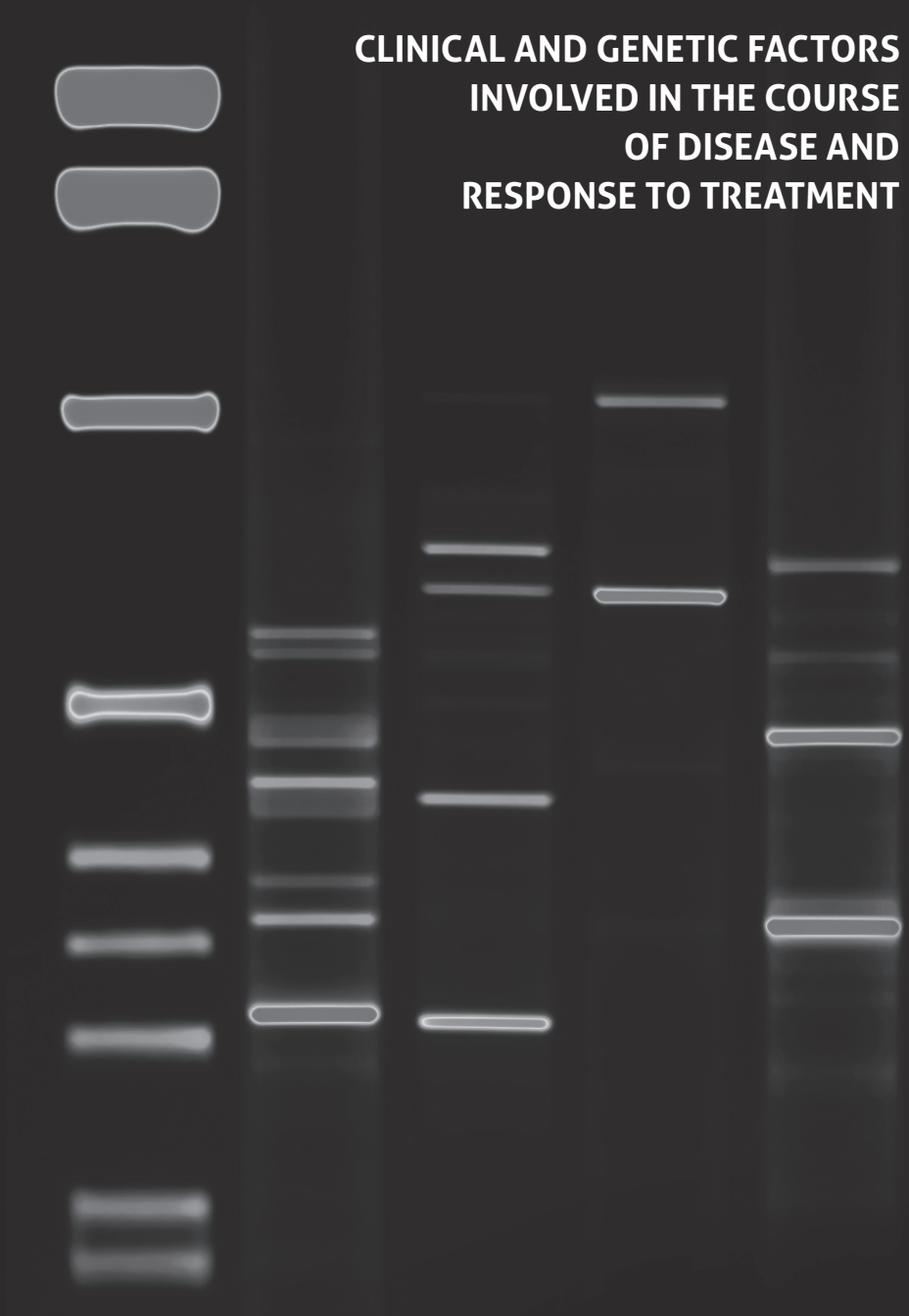
Author: Albers, Heleen Marion

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PART B

CLINICAL AND GENETIC FACTORS
INVOLVED IN THE COURSE
OF DISEASE AND
RESPONSE TO TREATMENT



CHAPTER 5

THE CLINICAL COURSE AND PROGNOSTIC VALUE OF DISEASE ACTIVITY IN THE FIRST TWO YEARS IN DIFFERENT SUBTYPES OF JUVENILE IDIOPATHIC ARTHRITIS

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H.M. Albers¹, D.M.C. Brinkman¹, S.S.M. Kamphuis², L.W.A. Suijlekom-Smit², M.A.J. van Rossum³, E.P.A.H. Hoppenreijs⁴, H.J. Girschick⁵, C. Wouters⁶, R.K. Saurenmann⁷, J.J. Houwing-Duistermaat¹, T.W.J. Huizinga¹, M.W. Schilham¹, R. ten Cate¹

1) Leiden University Medical Center, Leiden, the Netherlands.

2) Erasmus Medical Center- Sophia Children's Hospital, Rotterdam, the Netherlands.

3) Academic Medical Center- Emma Children's Hospital and Reade, location Jan van Breemen, Amsterdam, the Netherlands

4) Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

5) University of Wuerzburg, Wuerzburg, Germany.

6) University Hospital Gasthuisberg, Leuven, Belgium.

7) Zurich University Children's Hospital, Zurich, Switzerland

ABSTRACT

Objective

Juvenile Idiopathic Arthritis is a heterogeneous disease involving chronic arthritis. The clinical course is characterized by a fluctuating pattern of active and inactive disease. We have described in detail the clinical course in different JIA subtypes in the first two years after diagnosis and studied its relation to disease activity in the following years.

Methods

Detailed clinical data on different parameters describing the disease activity in sequential time periods covering the first two years after diagnosis were retrieved from the charts of 311 JIA patients and compared between subtypes. In a cohort of 146 patients the relation of these different clinical variables to the course of disease in the following three years was evaluated.

Results

The percentage of time with active disease in the first two years differed significantly between subtypes. In all subtypes a broad spectrum of activity was observed. The time with active disease in the first two years was the most significant factor associated with the duration of active disease in the following years.

Conclusion

In this study, different percentages of time with active disease have been observed between JIA subtypes in the first two years. The cumulative duration of activity varied widely within each subtype. Regarding the prognosis of the individual patient, the clinical course in the first two years appears to be predictive of the clinical course in the following years. Patients that have less time with active disease in the first two years are not likely to develop unremitting clinical course later on.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of disorders characterized by chronic inflammation of the joint. Seven different subtypes have been defined by the International League of Associations for Rheumatology (ILAR) based on clinical and laboratory parameters.¹ Within JIA, persistent oligoarthritis, extended oligoarthritis and rheumatoid factor (RF) negative polyarthritis are the most homogeneous subtypes with a large phenotypic overlap.² Although the remission rate is the highest in persistent oligoarthritis,³ the precise clinical course of the different subtypes is still unclear.

Prediction of the clinical course of the disease could be helpful for choosing the optimal treatment strategy for an individual patient. However, at this moment no clinically useful prognostic factors are known.^{4,5} The outcome of JIA regarding disease activity and remission has frequently been studied in the different subtypes, but unfortunately different studies have used a large variety of definitions of remission and thereby generated data that are difficult to compare.³⁻⁶ Several years ago a preliminary definition of remission has been formulated, defining different states of inactivity; inactive disease, clinical remission on medication and clinical remission off medication.⁷ Furthermore, almost all studies in JIA concerning outcome have used a cross-sectional study design, while Wallace et al clearly showed that JIA is a disease with fluctuating disease activity that can best be described by analysis of sequential time periods.⁸ By using sequential time periods, the cumulative time with active or inactive disease can be determined and used as outcome measure.^{8,9} Already different studies have shown that a prolonged disease activity is related to a poor outcome regarding radiographic damage.^{10,11} Moreover it seems to be important to distinguish between different states of activity, because reaching a state of minimal disease activity (MDA) is related to less damage to the joint (amongst others) compared to not reaching MDA.¹²

In this study we will describe the clinical course of the first two years after diagnosis in different subtypes of JIA by analyzing sequential episodes of disease activity. Moreover, we have studied the different parameters of disease activity assessed in the first two years after diagnosis in relation to the clinical course in the following years to identify clinical prognostic factors for the individual patient.

MATERIALS AND METHODS

Patient population

A cohort of 640 JIA patients, with oligoarthritis, polyarthritis and systemic JIA, originating from 7 different pediatric rheumatology referral centers in the Netherlands, Belgium, Germany and Switzerland and who were diagnosed after 1 January 1991, was observed retrospectively. For this study patients were excluded when no clinical data on disease activity were available ($n=144$), when the follow-up was less than 2 years ($n=158$), if re-classified with psoriatic arthritis, JIA with enthesitis and undifferentiated JIA ($n=6$) and if an ongoing uveitis was present with only a mild course of arthritis ($n=3$). This resulted in a JIA cohort of 311 patients that were included in the analysis of the clinical course of the first two years after diagnosis. In order to identify prognostic factors for the clinical course in the following years, only patients with a follow-up of ≥ 5 years were included ($n=146$), excluding 165 patients with a follow-up of >2 years and < 5 years. All patients were diagnosed or (re)classified according to the ILAR classification and had a self- or parental-reported Caucasian ethnicity.¹ The characteristics of the JIA patient cohort are listed in Table 1.

The ethical review boards of all participating centers gave their approval to this study and informed consent was obtained from all patients and/or parents.

Table 1. Patients' characteristics[#]

		n	(%)
Total JIA population		311	
Subtype:			
Persistent oligoarthritis		124	(39.9)
Extended oligoarthritis		56	(18.0)
RF- negative polyarthritis		91	(29.3)
RF- positive polyarthritis		9	(2.9)
Systemic JIA		31	(10.0)
Female		214	(68.8)
Follow-up (year)	(median; min-max)	4.8	2.0- 15.9
Age at onset (year)	(median; min-max)	4.1	0.6- 15.5
ANA	positive	163	(52.4)
	negative	109	(35.0)
	other*/ unknown	38	(12.2)
Uveitis	positive	47	(15.1)
	negative	225	(72.3)
	unknown	32	(10.3)

[#]) Parameters listed in numbers and percentages unless otherwise indicated

^{*)} If antinuclear antibodies are not consistently present or detected

Clinical data

Each patient's chart was reviewed retrospectively and the disease activity (according to different parameters) at all visits during the complete disease course was evaluated. We assumed that the patient stayed in the same state of disease activity until the next visit. Patients visited the pediatric rheumatologists with an interval of 6 months or less in case of inactive disease and with an interval of 3 months or less when disease was active. Due to the retrospective nature of this study, the follow-up of the patients has not been uniform; patients with a remitting course of disease had fewer visits to the pediatric rheumatologist than patients with an unremitting course of disease. However, when patients in an inactive state developed complaints the subsequent visit was usually placed forward. Therefore, in individual patients, mainly the state of active disease might be over-estimated.

Different parameters were used indicating disease activity; state of disease activity (active or inactive disease), the subjective physicians' global assessment of disease activity (categorized as: 0 = inactive disease, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe disease) and the number of joints with arthritis (categorized as: 0 = no joints, 1 = monoarthritis (1 joint), 2 = oligoarthritis ($\geq 1 - 4$ joints), 3 = polyarthritis ($\geq 4 - \leq 10$ joints), 4 = severe polyarthritis (> 10 joints)). No joint score was used for systemic JIA, because of the systemic features that are involved in JIA. Inactive disease was defined as absence of active arthritis, no systemic features, normal ESR (when available) and a physicians' global assessment indicating inactivity (category 0). The activity of JIA-associated uveitis was not incorporated in the definition of inactivity, because of missing data about the detailed ophthalmologic follow-up. However, to minimize the possible bias this could cause, we excluded patients ($n=3$) that had a known ongoing uveitis with only short periods of arthritis.

Furthermore, data on the use of different medication (yes/no) in the first two years were reviewed and grouped as: the use of non-steroidal anti-inflammatory drugs (NSAIDs) alone; intra-articular steroids (IAS) alone or combined with NSAIDs; sulfasalazine (SSZ) alone or in combination with NSAIDs; the use of Methotrexate (MTX) (started ≤ 6 months (early) or >6 months (late) after diagnosis) combined with any other (or no other) drugs besides Etanercept; Etanercept in combination with MTX and any other (or no other) drugs; other types or combinations of treatment.

Beside data on disease activity and medication, also data on the presence or absence of antinuclear antibodies (ANA), age at onset and gender were collected.

Parameters of activity

In order to evaluate the clinical course of the different subtypes, for each patient the first two years after diagnosis were analyzed. For this period, the percentage of time

with active disease was calculated together with the percentage of patients that had reached clinical remission within these first two years. Clinical remission (yes/no) was defined as the presence of an episode of inactivity lasting ≥ 6 months. Additionally, the mean physicians' global assessment and the mean joint score were calculated for each individual patient for the time the disease was active in the first two years (later referred to as the physicians' global assessment and joint score). The percentage of time with active disease that was evaluated as mild by the physicians (category 1) was used as measure for mild active disease. These different parameters of disease activity were compared between the different subtypes.

To study the prognostic value of different clinical parameters assessed in the first two years, the percentage of time with active disease in the following three years (third, fourth and fifth year (3-5) after diagnosis) was calculated to determine the clinical course later on in the disease. The percentage of time with active disease during the years 3-5 was used to define remitting and unremitting clinical course. Remitting clinical course was defined as: percentage of time with active disease between 0 and 35%, whereas unremitting clinical course was defined as: percentage of time with active disease $\geq 65\%$. Patient with active disease during more than 35% and less than 65% of the time were considered as having an intermediate clinical course. Following the same definition, patients were also categorized into remitting, intermediate and unremitting course according to their percentage of active disease in the first two years after onset.

Statistical analysis

When analyzing the parameters of activity in the first two years in different subtypes, non-parametric tests (Kruskal Wallis, Mann-Whitney U test) were used because of the non-normal distribution of different variables in the overall population and some subtypes. Comparing the different parameters in patients with a remitting and unremitting clinical course, a Pearson's Chi-square or Mann-Whitney U test were used depending on the tested variable. A p-value of <0.05 was regarded as statistically significant.

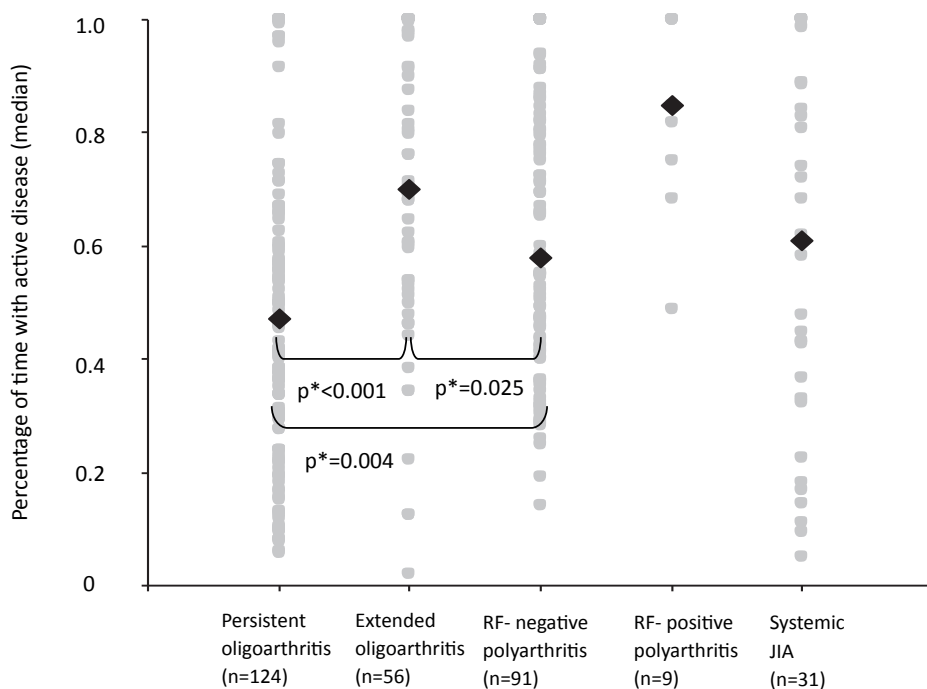
Positive and negative predictive values were calculated for the remitting and unremitting category comparing the clinical course in the first two years after onset with the clinical course in the years 3-5 in order to estimate the predictive value of the clinical course in the first two years. Data were analyzed using SPSS 16.0.

RESULTS

Percentage of time with active disease in the first two years

The percentages of time with active disease in the first two years after diagnosis in the overall JIA cohort as well as in the individual subtypes are listed in Table 2 and shown in Figure 1. The median percentage of time with active disease in the overall JIA cohort is 57%, meaning that half of the patients have more than 14 months of active disease (cumulative) during the first two years. The percentage of time with active disease is significantly different between the subtypes ($p=0.031$). Analyzing the three subtypes with the most phenotypic overlap (persistent oligoarthritis, extended oligoarthritis and rheumatoid factor (RF) negative polyarthritis), the lowest median percentage of time with active disease is observed in patients with persistent oligoarthritis (47%) compared to extended oligoarthritis (70%; $p<0.001$) and RF- negative polyarthritis (58%; $p=0.025$).

Figure 1. The percentage of time with active disease in the first two years after diagnosis in the different subtypes.



◆ median percentage of time with active disease per subtype of JIA

*) p-value of Mann-Whitney U test comparing two subtypes (persistent oligoarthritis vs extended oligoarthritis, extended oligoarthritis vs RF-negative polyarthritis, persistent oligoarthritis vs RF-negative polyarthritis)

$p=0.004$), whereas the median percentage of time with active disease in extended oligoarthritis is the highest and significantly different from RF-negative polyarthritis ($p=0.025$). In patients with systemic JIA the median percentage of active disease is comparable to patients with RF-negative polyarthritis (61%; $p=0.67$). Patients with RF-positive polyarthritis have the highest median percentage of time with active disease (85%), but because of the small sample size ($n=9$) no reliable conclusion can be drawn from these data.

Clinical remission in the first two year

When an episode of inactive disease lasted ≥ 6 months, this was regarded as an episode of clinical remission. The percentage of patients within the different subtypes who reached clinical remission in the first two years is listed in Table 2. Patients with extended oligoarthritis have a significantly lower percentage of clinical remission (36%) compared to both persistent oligoarthritis (69%; $p < 0.001$) and RF-negative polyarthritis (60%; $p = 0.004$). No difference between persistent oligoarthritis and RF-negative polyarthritis patients was observed ($p=0.22$). In systemic JIA, 58% of the patients have reached clinical remission in the first two years. Inherent to the high percentage of time with active disease, the percentage of clinical remission is low (11%) in RF-positive polyarthritis. Only 84 patients had a continuous period of inactive disease for ≥ 12 months in these first two years and 34 patients (of which 68% persistent oligoarthritis patients) were off medication for ≥ 12 months in that episode.

Physicians' global assessment of disease activity, percentage of mild active disease and the joint score in the first two years

The physicians' global assessment (reviewed at times when the disease was active in the first two years) in the overall JIA cohort and in the different subtypes is listed in Table 3. No significant differences in the median physicians' global assessment of disease activity were observed when comparing only persistent oligoarthritis, extended oligoarthritis and RF-negative polyarthritis ($p=0.58$). This means that although the cumulative time of active disease is different in these three subtypes, the physician evaluates the severity of disease activity similar at times when the disease is active. No association between the percentage of time with active disease and the physician's global assessment is observed in the analysis of the total JIA cohort (data not shown). The percentage of time in which the physicians' global assessment is evaluated as mild (category 1) is also listed in Table 3. No significant differences in percentages of mild active disease are observed comparing JIA subtypes.

Due to the ILAR classification that is based on differences in the number of affected joints, the median joint score during active disease in the first two years is signifi-

Table 2 The percentage of time with active disease and the percentage of patients that have reached clinical remission in the first two years after diagnosis in the overall JIA cohort and the different subtypes.

	Percentage of time with active disease		Clinical remission °	
	median (range)	p ¹	%	p ²
Overall JIA cohort (n=311)	0.57 (0.02-1.0)	0.031 (1-5)	0.58	< 0.001 (1-5)
1.Persistent oligoarthritis (n=124)	0.47 (0.06- 1.0)	<0.001 (1vs 2)	0.69	<0.001 (1 vs 2)
2.Extended oligoarthritis (n=56)	0.70 (0.02- 1.0)	0.025 (2 vs 3)	0.36	0.004 (2 vs 3)
3.RF- negative polyarthritis (n=91)	0.58 (0.14- 1.0)	0.004 (1vs 3)	0.60	0.218 (1 vs 3)
4.RF- positive polyarthritis (n=9)	0.85 (0.49- 1.0)		0.11	
5.Systemic JIA (n=31)	0.61 (0.05- 1.0)	0.67 (3 vs 5)	0.58	0.269 (1 vs 5)

°) percentage of patients that have reached clinical remission in the first two years after diagnosis

- 1) p-value of Kruskal-Wallis test in all subtypes (1-5) or Mann-Whitney U test comparing two subtypes (persistent oligoarthritis vs extended oligoarthritis, extended oligoarthritis vs RF-negative polyarthritis, persistent oligoarthritis vs RF-negative polyarthritis) indicated by numbers (in brackets).
- 2) p-value of Pearson-Chi-square comparing the percentage of clinical remission in all subtypes (1-5) and comparing the subtypes indicated by numbers (in brackets).

cantly different between the subtypes (Table 3). Patients with an extended oligoarthritis have a significant higher median joint score than persistent oligoarthritis patients, although both subtypes have ≤ 4 joints involved in the first 6 months. This indicates that extended oligoarthritis not only affects more than 5 different joints during the disease course, but that on the average more joints are active at the same time.

These data show that the clinical course, indicated by the percentage of time with active disease in the first two years after diagnosis, is different in the JIA subtypes. Especially the clinical course of persistent oligoarthritis is significantly different from extended oligoarthritis, which seem to be two separate entities. However within each subtype an individual patient can have a wide range of activity varying from only a short time of active disease to ongoing disease activity. This already shows that the subtype JIA on itself is not valid as a prognostic factor for the individual patient.

Prognostic factors for the clinical course in years 3-5 after diagnosis

In patients with a follow-up of ≥ 5 years (n=146) the percentage of time with active disease was evaluated during the years 3-5 (third, fourth and fifth year) after diagnosis and patients were categorized into a remitting (0-35% time with active disease), intermediate (35-65%) or an unremitting clinical course (65-100%). The different parameters of disease activity measured in the first two years, the use of medication in the first two years together with subtype, age at onset, gender and ANA status were

Table 3 The physicians' global assessment, the percentage of time with mild active disease and joint score in the first two years after diagnosis, all reviewed only over the time when disease was active.#.

	Physicians' global assessment ^{*,}		Percentage of time with mild active disease		Joint score ^o	
	median (range)	p ¹	median (range)	p ¹	median (range)	p ²
Overall JIA cohort (n=266/261)	1.74 (1.0- 3.38)	0.031 (1-5)	0.33 (0- 1.0)	0.203 (1-5)		
1.Persistent oligoarthritis (n= 97/95/ 124)	1.70 (1.0- 2.62)	0.583 (1-3)	0.41 (0- 1.0)	0.885 (1-3)	1.30 (1.0- 2.31)	<0.001 (1 vs 2)
2.Extended oligoarthritis (n=49/48/56)	1.74 (1.0- 3.0)		0.34 (0- 1.0)		1.82 (0.61- 3.0)	0.023 (2 vs 3)
3.RF negative polyarthritis (n=80/78/91)	1.74 (1.0- 2.72)		0.33 (0- 1.)		2.45 (1.69- 4.0)	0.012 (3 vs 4)
4.RF positive polyarthritis (n= 9/9/9)	2.00 (1.08- 2.73)		0 (0- 0.92)		3.00 (1.37- 3.0)	
5.Systemic JIA (n= 31/31/31)	1.87 (1.07- 3.38)		0.18 (0- 0.93)			

^{*)} The physicians' global assessment of disease activity is categorized as: 0 = inactive disease, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe disease.
^{o)} The joints score is categorized as: 0 = no joints, 1 = monoarthritis (1 joint), 2 = oligoarthritis (>=1 - 4 joints), 3 = polyarthritis (>=4- <=10 joints), 4 = severe polyarthritis (> 10 joints) and in case of systemic JIA an additional category 5 = systemic features.
1) p-value of Kruskal-Wallis test in all subtypes (1-5) or in persistent oligoarthritis, extended oligoarthritis and RF-negative polyarthritis (1-3).
2) p-value of Mann-Whitney U test. Subtypes that are being compared are indicated by numbers (in brackets).

Table 4. Patients' characteristics and comparison of the different clinical and demographic parameters between patients with a remitting course and an unremitting course #

	n	Remitting course*	Unremitting course*	p
All JIA subtypes*	146	62 (42.5)	44 (30.1)	
Subtype ^o				0.418 ¹
Persistent oligoarthritis	43	25 (58.1)	10 (23.3)	
Extended oligoarthritis	44	15 (34.1)	14 (31.8)	
RF negative polyarthritis	39	15 (38.5)	12 (30.8)	
RF positive polyarthritis	4	0 (0)	4 (100)	
Systemic JIA	16	7 (43.8)	4 (25.0)	
Age at onset (years), median (range)	146	2.94 (0.62-12.64)	4.17 (1.23- 14.2)	0.203 ²
Gender				
female	108	46 (42.6)	33 (30.6)	
male	38	16 (42.1)	11 (28.9)	0.96 ¹
ANA†				0.437 ¹
positive	83	37 (44.6)	22 (26.5)	
negative	34	12 (35.3)	13 (38.2)	
Percentage active disease in first two years, median (range)	106	45.8 (6.22- 100)	100 (47.4- 100)	<0.001 ^{2§}
Clinical remission (>= 6 months) in first 2 years (yes/no)	69	45 (65.2)	8 (11.6)	<0.001 ^{1§}
Clinical remission off medication (>= 12 months) in the first 2 years (yes/no)	10	9 (90)	0	<0.001 ^{1§}
Physicians' global assessment in first two years, median (range) ^o	122	1.70 (1.0- 3.0)	1.74 (1.0- 2.72)	0.373 ²
Percentage mild active disease	119	0.34 (0- 1.0)	0.37 (0- 1.0)	0.941 ²
Medication in first two years:				
NSAIDs only	35	21 (60.0)	8 (22.9)	0.052 ¹
IAS ³	29	19 (65.5)	4 (13.8)	0.017 ^{1§}
SSZ ³	9	3 (33.3)	1 (11.1)	0.171 ¹
MTX ⁴	47	14 (29.8)	19 (40.4)	0.074 ^{1§}
MTX early	13	5 (38.5)	6 (46.2)	0.396 [§]
MTX late	34	9 (26.5)	13 (38.2)	
Etanercept ⁵	6	1 (16.7)	4 (66.7)	0.120 ¹
Systemic glucocorticoids ⁶	39	11 (28.2)	17 (43.6)	0.042 ^{1§}

NSAIDs= non-steroidal anti-inflammatory drugs, IAS= intraarticular steroids, SSZ= sulfasalazine, MTX= methotrexate

#) Parameters listed in number (percentage) unless otherwise indicated.

*) Remitting and unremitting course based on the disease activity in the years 3-5 after diagnosis.

•) According to the revised ILAR classification (1)

o) Patients with RF-positive polyarthritis not included in the analysis of subtypes because of the low number of patients.

1) p-value of Pearson's Chi-square

2) p-value of Mann Whitney U test

†) Analysis of ANA only in persistent oligoarthritis, extended oligoarthritis and RF- negative polyarthritis.

§) p-value of <0.05 statistical significant

§) calculated over the time when disease was active

3) monotherapy or combined with NSAIDs

4) monotherapy or combined with other drugs besides Etanercept

§) Difference between MTX early and late

5) always combined with MTX

6) monotherapy or combined with other drugs

compared between the group of patients with a remitting and unremitting clinical course in years 3-5 in order to evaluate their relation to the clinical course (Table 4).

A remitting clinical course during the years 3-5 was observed in 42.5% of the patients compared to 30.1% of patients with an unremitting disease course. No differences in age at onset, gender and ANA status were observed between patients with a remitting course and those with an unremitting course. When analyzing the different subtypes, the patients with RF-positive polyarthritis were excluded because of their small sample size. No difference in the percentage of remitting and unremitting clinical course was observed between the remaining subtypes. When the use of medication in the first two years was analyzed, it appeared that patients who had received only intra-articular steroids (combined with NSAIDs) as treatment showed more often a remitting clinical course ($p=0.017$), while patients that were treated with systemic glucocorticoids had a higher percentage of unremitting clinical course ($p=0.042$).

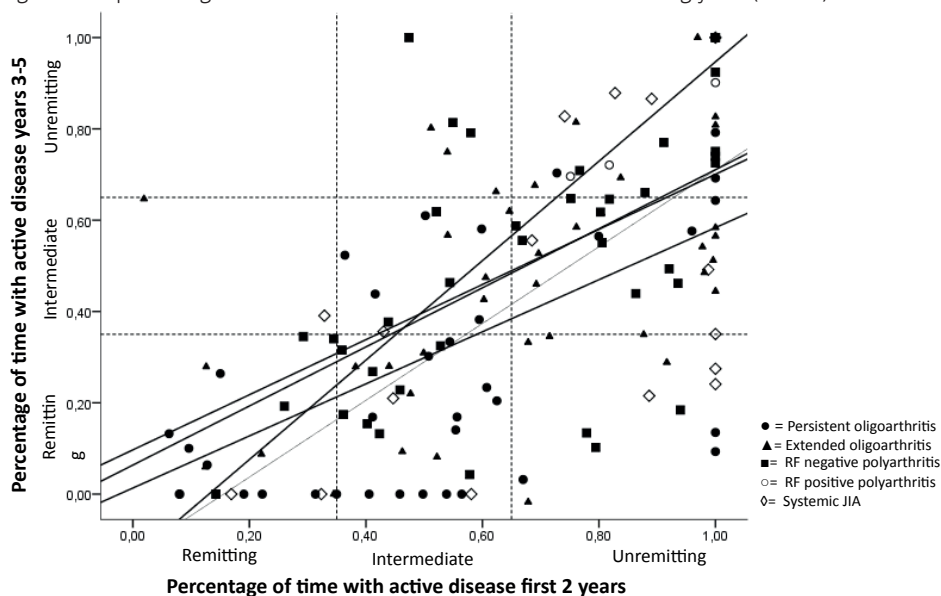
Most important, already in the first two years after diagnosis the percentage of time with active disease was significantly lower and the percentage of patients reaching clinical remission significantly higher in patients who had a remitting clinical course in the following years (years 3-5) ($p<0.001$). During the first two years, there were no differences in physicians' global assessments or percentage of time periods with mild active disease observed between the patient groups with a remitting or unremitting course in year 3-5. This might indicate that reaching a state of inactive disease instead of a diminished disease activity should be the goal of treatment in JIA.

Predictive value of the percentage of active disease during the first 2 years

Figure 2 shows the percentage of time with active disease in the first 2 years plotted against the activity in the years 3-5. A significant correlation between the two variables is observed both in the overall JIA population as well as in each subtype ($p < 0,05$; data not shown). The percentage of active disease in the first two years was categorized into remitting, intermediate and unremitting course (following the same definition as used for years 3-5), and compared to the clinical course in years 3-5 (Figure 2 and Table 5). Furthermore the positive and negative predictive values of having a remitting or unremitting course in the first two years after diagnosis in relation to the course in years 3-5 are listed in Table 5. The positive predictive value of having a remitting disease in the first two years of disease was 90.9%, whereas the negative predictive value of having an unremitting clinical course in the first two years is 91.3%.

Analyzing the clinical variables assessed in the first two years and their association with activity of the longer term (years 3-5) resulted in a significant association

Figure 2. The percentage of time with active disease in the first 2 years after diagnosis plotted against the percentage of time with active disease in the three following years (n=146).



----- lines indicating the criteria for a remitting, intermediate and unremitting clinical course

— regression lines of the different subtypes (all $p < 0.05$)

Table 5. Categorized clinical course of first two years against the clinical course of the following three years

Activity first 2 years	Activity year 2-5			Positive predictive value	Negative predictive value
	Remitting	Intermediate	Unremitting		
Remitting	20 (90.9)	2 (9.1)	0 (0)	90.9	66.1
Intermediate	28 (59.6)	13 (27.7)	6 (12.8)		
Unremitting	14 (18.2)	25 (32.5)	38 (49.4)	49.4	91.3

between the time with active disease in the first 2 years and the duration of active disease in the following three years. Patients with a remitting course in the first two years are not likely to develop a more severe course, whereas patients categorized as having no unremitting course are not likely to develop an unremitting course. It seems that the disease activity (category) in the first two years can be used as predictive factor for the disease in the following years.

DISCUSSION

This study shows that the clinical course, indicated by the percentage of time with active disease in the first two years after diagnosis, is different in the JIA subtypes. Patients with extended oligoarthritis seem to have the most severe clinical course with respect to time with active disease and not achieving remission, compared to patients with persistent oligoarthritis and RF-negative polyarthritis and should be regarded as a separate entity. This higher percentage of active disease in extended oligoarthritis might be due to less aggressive treatment; significant less patients with extended oligoarthritis received methotrexate in the first two years (38%), compared to RF-negative polyarthritis patients (65%; $p=0.002$). This suggests that extended oligoarthritis patients should be treated more aggressively and/or earlier in their clinical course.

The observed disease activity in the RF-positive polyarthritis patients is the highest of all, but because of the small number of patients included in this study, no conclusions can be drawn concerning this subtype. The percentage of time with active disease in the different subtypes in this cohort of JIA patients is similar to the percentages of active disease that are described by Wallace et al and Oen et al.^{8,9} These similarities suggest that the percentage of active disease is representative for the different subtypes and a reproducible measure for sequential disease activity during the course of the disease.

In the systemic JIA subtype it is already known that a broad spectrum of disease activity with a monocyclic or intermittent course as well as an unremitting disease courses exists. Moreover, in all subtypes a broad spectrum of disease activity is observed in individual patients, varying from a small percentage of time with active disease to no inactive episodes at all. For the individual patient it would be more relevant to identify clinical prognostic factors that are associated with a remitting or unremitting clinical course.

In this study different clinical parameters have been tested for their association with the clinical course in the years 3-5 after diagnosis. We have chosen assess these different parameters in the first two years after diagnosis. We assumed that a minimum of two years are required after diagnosis to treat the patient with the optimal medication and evaluate its effectiveness and therefore this period might give a good representation of the disease activity after onset in the individual patient. In all subtypes the percentage of active disease in the first 2 years after diagnosis is strongly associated with the clinical course in the following three years and can reliably be used to identify patients with a remitting or a non-unremitting clinical course. We have defined the clinical course based on the percentage of time with active disease; patients with an unremitting course having active disease 65-100%

of the time, thus only a short time with disease quiescence. It should be noted that no detailed information about the activity of a JIA-associated uveitis was available, so patients with inactive disease could be having an active uveitis. However, patients with only mild arthritis and an ongoing severe uveitis were excluded from the study. In contrast to the study of Oen et al, in this study no associations between subtype, ANA status and age at onset and the clinical course were observed.¹³ Association with the types and symmetry of joints involved at disease onset was not studied because of the lack of detailed data on joint involvement.

Our data show that in the overall JIA population up to 30% of the patients have an unremitting clinical course in the years 3-5 after diagnosis, indicating that the treatment regime used in this patient cohort is not sufficient to induce long lasting disease quiescence. However patients included in this study having a follow-up of ≥ 5 years were diagnosed before May 2003 and only 6 patients used Etanercept and no patients used other biologicals. In the last years more patients have efficiently been treated with Etanercept and other biologicals like IL1-receptor antagonist or anti IL-6.¹⁴ Future studies should be performed to evaluate the clinical disease course of patients treated with these drugs.

In conclusion, differences in percentages of active disease between JIA subtypes have been observed, but more important; within each subtype individual patients can have both a remitting or unremitting clinical course. For the individual patients the clinical course in the first two years after diagnosis is clearly related to the clinical course in the following three years. Studies in rheumatoid arthritis show that reaching sustained remission early in the course of disease by using a more aggressive initial treatment is related to an improved radiographic outcome and less joint damage.¹⁵⁻¹⁷ This study shows that a lower percentage of active disease in the first two years is related to a mild course of disease afterwards. Also in JIA, reaching a state of clinical remission early in the course of disease should be the aim for treating patients and therefore a more aggressive initial treatment might be necessary. Future studies are needed to identify prognostic factors that could already be determined at disease onset and could reliably point out the patients that are at risk of an unremitting disease course and should be treated with early aggressive treatment.

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