UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Département femme-mère-enfant

Master thesis in medicine No 5486

Disease evolution in systemic-onset juvenile idiopathic arthritis: Results from the JIRcohorte

Student
Wallimann Michelle

First supervisor
Prof. Dr. med. Hofer Michaël
Pediatric Rheumatology Department, CHUV

Second supervisor
Dr. med. Theodoropoulou Katerina
Pediatric Rheumatology Department, CHUV

Expert
Prof. Dr. med. Spertini François
Allergology and Immunology Department, CHUV

Lausanne, 12.12.2018

Acknowledgments

I would first like to thank my supervisor, Professor Dr. med. Michaël Hofer. He supported me from the beginning in finding the theme of this thesis throughout the multiple moments of questions and insecurities. I would specially thank Prof. Hofer for the great encouragement to apply for different academic events, which allowed me to experience several amazing moments in this new world of clinical research.

I would also like to thank my co-supervisor, Dr. med Katerina Theodoropoulou. She was always my direct contact person and responded always to my hundreds of questions. Furthermore, I did learn from her how clinical research is functioning and how amazing it can be. I am very grateful for that.

I would also like to thank the expert involved in the validation process of this thesis, Professor Dr. med. François Spertini.

I would like to thank all the children and parents participating in the cohort study, allowing us to do this research. And I would also like to thank all the participating centers in the Juvenile Inflammatory Rheumatism Cohort, without them, this multicenter study would have been impossible.

Finally, I must express my very profound gratitude to my family and my partner for all the support and motivation throughout my years of study and the process of this thesis. This accomplishment would not have been possible without them. Thank you.

Wallimann Michelle

Abstract

Introduction
Systemic-onset juvenile idiopathic arthritis (SoJIA) is a potentially severe disease with both systemic and joint inflammation; different evolutive forms were described (monophasic, polyphasic or persistent), but the outcome is hardly predictable at diagnosis.
This study aims to identify early predictors of disease evolution within the SoJIA population enrolled in the Juvenile Inflammatory Rheumatism cohort (JIRcohorte), an international prospective cohort study.

Method
104 SoJIA patients with a minimum of two-year follow-up were enrolled. 59 patients were excluded due to loss to follow-up, consent withdrawal or incomplete information on disease activity. Demographics, clinical data and disease activity were collected (retrospectively if diagnosis < 2015 and prospectively if diagnosis ≥ 2015) and described for 45 patients. At diagnosis, median age and disease duration was 4.75 years and 1.0 months, respectively, male to female ratio was 1:1.6. Median follow-up was 5.02 years. 41 and 31 patients were treated with biologics and Disease Modifying Anti-Rheumatic Drugs (DMARDs), respectively.
We present the results in 45 patients with complete data for disease activity and medication use.

Results
Corresponding to their evolution, patients were classified in the monophasic (n=12), polyphasic (n=17) or persistent group (n=16). Females were predominant in the monophasic and polyphasic group with 91.7% and 58.8%, respectively. Initial clinical presentation was characterized by fever for nearly all children (97.8%), other systemic symptoms were much less frequent. Possible predictors were first analyzed by univariate logistic regression comparing persistent disease evolution with non-persistent disease evolution (i.e. monophasic and polyphasic). Polyarthritis at 6-months and arthritis at 12-months post-diagnosis was both significantly more frequent in the persistent disease evolution group 18.8% vs. 3.4%; $p < 0.05$ and 56.3% vs. 13.8%; $p < 0.01$, respectively. Patients having a delay between symptom onset and diagnosis (> 2 months) were significantly more frequent in the persistent disease evolution group. The rate of elevated laboratory inflammatory markers at 6- and 12- months was significantly higher in the persistent group as well (ESR ≥ 26 mm/h: 37.5% vs. 3.4%, $p < 0.01$; CRP > 10 mg/L: 62.5% vs. 13.8%, $p < 0.01$). Furthermore, the treatment frequency with DMARDs and the treatment duration of more than six months was both significantly higher in the persistent group 93.8% vs. 55.2%; $p < 0.05$ and 93.7% vs 41.4%; $p < 0.05$, respectively.

Conclusion
Active arthritis as well as elevated inflammatory markers throughout the first year of disease are possible predictors of a persistent disease course. Furthermore, the delay between symptom onset and diagnosis (> 2 months) is suggesting a persistent disease evolution. The persistent disease evolution correlates with a more severe disease course. Therefore, it is expectable that the type of medication used, and its duration are more severe as well. The multivariate model did not show any statistically significant difference between the persistent vs. non-persistent group. We have further validated the existence of three clinically discernable disease evolution types in SoJIA, which may be predicted at diagnosis by several clinical features. Further research should concentrate on standardized data collection in multicenter cohort studies to generate enough statistical power to confirm or reject the presented tendencies within this study.

Keywords: systemic juvenile idiopathic arthritis; disease evolution; outcome

Table of content

List of tables

List of figures

Introduction

Historical preamble. In 1897 George Frederic Still published the first description of, what we know today as, systemic-onset juvenile idiopathic arthritis (SoJIA). The eponymous "Still's disease" endures in the name for its adult-onset form (adult-onset Still's disease, AOSD). In his work "On a form of chronic joint disease in children", he painted a detailed picture of the clinical presentation of twelve patients with articular inflammation, splenomegaly and lymphadenopathies. He was also the first to comment on the disease course of SoJIA, concluding that: *"The course of these cases is slow. Improvement may occur for a time under treatment or spontaneously, but the disease soon progresses again until a condition of general joint disease is reached which seems to be permanently stationary."*(1)

Classification. SoJIA is categorized among a heterogeneous group of pathologies termed "juvenile idiopathic arthritis" (JIA) which includes all pediatric rheumatic diseases of unknown origin that present with a persistent (> six weeks) arthritis before the age of sixteen years. At the beginning of the 21st century, the International League of Associations for Rheumatology (ILAR) classified seven JIA subtypes in the aim of creating a common nomenclature. The seven subtypes are Systemic Arthritis (SoJIA), Oligoarthritis, Polyarthritis (Rheumatoid Factor Negative), Polyarthritis (Rheumatoid Factor Positive), Psoriatic Arthritis, Enthesitis Related Arthritis, Undifferentiated Arthritis. SoJIA is distinguished from other JIAs due to its particularity of having a variety of systemic symptoms. To fulfill the ILAR criteria for SoJIA, the patient should present a persistent (> two weeks) undulating fever with a paroxysmal pattern, accompanied by oligo- or polyarthritis and either rash, lymphadenopathy, serositis (i.e. pericarditis, pleuritis or peritonitis) or organomegaly (hepato- and/or splenomegaly).(2) Patients are also at risk of developing potentially fatal systemic inflammatory complications (such as macrophage activation syndrome(3)), which has resulted in SoJIA having the highest mortality rate (3.9/1000 person years (4)) of all JIA subtypes.

Despite recent medical advances, SoJIA remains a diagnosis by exclusion, where its heterogeneous and nonspecific clinical presentation, as well as the lack of specific laboratory markers, create difficulties for a rapid and accurate diagnosis. SoJIA reportedly accounts for 10% of all JIA cases in Europe, however its impact is likely under-represented due to these problematic diagnostic criteria (5,6).

Clinical presentation. Behrens et al. studied the clinical presentation of SoJIA in 136 children and found significant variation among initial presentations of the case-defining symptoms,

which could range from isolated occurrences of a single symptom to various, life-threatening combinations. However, only a small percentage presented with the ILAR criteria necessary for SoJIA classification: a weakness that was already reported by Hofer et al. in 2001.(7) The most frequent symptoms at first presentation were fever followed by arthritis and cutaneous rash, all diagnosed in over 75% of the children included. Lymphadenopathies, organomegalies and pericarditis were seen in much fewer patients. Articular involvement was oligo- or polyarticular in over 80% of cases, whereas the most frequent joints involved were the wrists, knees and ankles.(8)

Cytokine profile. SoJIA is a complex autoinflammatory disease with a cardinal implication of the innate immune system. Neutrophils, monocytes and macrophages are predominantly activated, resulting through different pathways in the excess of pro-inflammatory cytokines, mostly Interleukin 1β (IL-1β), Interleukin 18 (IL-18) and Interleukin 6 (IL-6). IL-1β has a well-known pro-inflammatory activity. In 2001, Pascual et al. documented the overexpression of IL-1β in SoJIA by showing its secretion from healthy Peripheral Blood Mononuclear Cells (PBMC) after incubation with the serum of SoJIA patients. (9) Furthermore, the efficacy of anti-IL1 drugs underlines the important role of this cytokine in the pathophysiology of SoJIA. (10,11) In addition, anti-IL6 treatment has a well reported efficacy in SoJIA patients, supporting its implication in the disease. (12,13) IL-18, a proinflammatory cytokine of the IL-1 family, has a crucial role in the pathophysiology of SoJIA. Lotito et al. showed much higher levels of IL-18 in synovial fluid of SoJIA patients compared to other JIA patients. (14) Furthermore, Weiss et al. proposed an association between the macrophage activation syndrome, a potentially fatal complication of SoJIA, and chronically elevated IL-18 levels. (15) Interleukin 10 (IL-10) has an anti-inflammatory role and hypotheses are, that IL-10 may be defective or insufficient in SoJIA patients, failing to counterbalance the pro-inflammatory mechanism.(16) Interleukin 17 (IL-17), Tumor necrosis factor-α (TNF-α) and Interferon-γ (INF- γ) are cytokines that are implicated with an undetermined or controversial role in the pathophysiology of SoJIA. (17,18)

Treatment. First-line therapies include Non-Steroidal Anti-Inflammatory Drugs (NSAID) and glucocorticoids. In recent years, great advances have been made in identifying the potential mediators of the underlying immunological pathology, such as IL-1β and IL-6. (9,19) Biological agents targeting these immune pathways have since shown promise in several randomized controlled clinical trials. Notably, Anakinra (Anti-IL 1 receptor-antagonist), Canakinumab (Anti-IL1β antibody) and Tocilizumab (Anti-IL6R antibody), which have all since been incorporated into the standard therapeutic SoJIA regimen. (10–12) Current research concentrates on

identifying new cytokine targets, such as the inhibition of Interleukin 18 (IL-18), an important pro-inflammatory cytokine of the IL-1 family. Recent results of the first clinical study testing the recombinant human IL-18 binding protein in adults showed good response and a favorable safety profile in AOSD patients. (20) Today's research is concentrated on evaluating not only their efficacy but also their safety by designing prospective cohort studies enabling long term monitoring of adverse effects that were not captured in the shorter efficacy studies. (13,21,22)

Disease evolution and outcome. Morbidity in SoJIA is largely defined by the functional limitations of destructive arthritis. Spiegel et al. identified thrombocytosis and persistent active systemic disease (six months after onset) as strong predictors for a poor functional outcome. (23) Persistent active systemic disease has proven to be a particularly important prognostic marker. (24,25) Lomater et al. first described the different patterns of disease evolution as monocyclic, intermittent and persistent. (24) Singh-Grewal et al. are one of the few groups to examine the predictors of the disease evolution in SoJIA. According to them, the only factor at diagnosis that is predictive of a non-monophasic (i.e. intermittent or persistent) evolution was the presence of a polyarticular arthritis. They described additional predictors of a non-monophasic course at three months (i.e. fever and active arthritis) and six months post diagnosis (i.e. erythrocyte sedimentation rate (ESR) > 26 mm/hour and the persistent use of corticosteroids).(26) So far, our knowledge of the early predictors in SoJIA disease evolution is based on very limited data, which is fractured across groups with varying diagnostic definitions.

Objectives. This retrospective cohort study aims to identify early predictors of SoJIA disease evolution using standardized classifications. We provide detailed diagnostic phenotypes of 45 enrolled patients including clinical, laboratory and treatment variables. We then examine univariate and multivariate correlations of these variables with the disease progression. The second aim is to describe the disease evolution within this international SoJIA population.

Materials and methods

Cohort and study design. A multicenter retrospective observational study was conducted on 45 patients enrolled in the Juvenile Inflammatory Rheumatism cohort (JIRcohorte). 104 patients were recruited and followed at the participating pediatric rheumatology tertiary referral centers (Pediatric Immunology and Rheumatology Romande (n=17), University Children's Hospital Zurich (n=9), Lugano Regional Hospital (n=1), Children's Hospital Ibnou Rochd Casablanca (n=15), Hôpital Femme Mère Enfant University Hospital Lyon (n=33), Hôpital d'Estaing, University Hospital Clermont-Ferrand (n=6), University Hospital Nantes (n=2), University Hospital Leuven (n=21).

Patients were considered eligible if diagnosed as having SoJIA using an expert opinion and/or the ILAR criteria(2) and complete information on disease activity. Signed informed consent was provided by all legal guardians and by older children with age-adapted consent forms. Inclusion required a minimum two-year follow-up participation. 42 patients were excluded due to consent withdrawal or loss-to-follow-up. Seventeen patients were excluded due to incomplete information on disease activity. Expert opinion is defined as high clinical and laboratory suspicion of SoJIA by an experienced pediatric rheumatologist without fulfilling all necessary ILAR criteria.

The JIRcohorte is an observational prospective inception cohort study developed to promote multicentric international studies on juvenile inflammatory rheumatisms aiming a better understanding of these rare diseases and their therapies. More than twenty participating centers in France, Switzerland, Belgium and Morocco contribute to the data collection. Prospective data collection started in 2015. Patients are enrolled when having a juvenile inflammatory rheumatism and a signed informed consent.

Data collection. Data, concerning information from 2005 until 2014, was systematically collected in the JIRcohorte platform by consulting patient dossiers. Data concerning information from 2015 until August 2018 was prospectively entered in the JIRcohorte platform. Missing data from 2015 until 2018 was retrospectively entered by consulting patient dossiers. Data collected included demographic information such as sex, origin, age at disease onset, and age at diagnosis. Clinical signs and symptoms included joint count (i.e. number of joints with arthritis), and binary variables for the presence of enthesitis, arthralgia, fever, rash, lymphadenopathy, hepatomegaly, splenomegaly and serositis. Additionally, laboratory results [Elevated Sedimentation Rate (ESR), C reactive protein (CRP)] and detailed medication use were also captured.

Disease evolution was observed at 6 months post-diagnosis and then annually by following the assessment of the disease status by the pediatric rheumatologist (i.e. classification into either inactive disease, continued activity or flare). Clinically inactive disease is defined using the following criteria proposed by Wallace et al.: absence of systemic symptoms (fever, rash, organomegaly, or generalized lymphadenopathy), absence of active arthritis and uveitis, normal ESR or CRP results, physician's global assessment of disease activity at the best possible score for the instrument used (e.g. Visual Analogue Scale at 0 cm) and duration of morning stiffness of ≤ 15 minutes. (27) A flare is defined as reoccurrence of one of the previously defined variables. Remission is defined as twelve months of clinically inactive disease. (28) The monophasic disease course in this study is defined as the occurrence of active disease (systemic symptoms and/or arthritis) followed by inactive disease without recurrence. By this definition, remission is obtained within 2 years. The polyphasic course is defined by the recurrence of active disease at any time after having achieved inactive disease. A persistent evolution is characterized by the persistence of systemic symptoms and/or arthritis and/or abnormal laboratory results for at least 24 months.

Primary data analysis.

Demographic and clinical data were summarized by their frequencies and percentages. Continuous variables are represented by their medians and interquartile range.

Analysis of variance (ANOVA) was performed to assess differences of clinical, laboratory and therapy features between the three disease evolution groups (i.e. monophasic, polyphasic and persistent).

Univariate and multivariate logistic regression was performed to assess the association between each predictor and the outcome of persistent disease evolution at diagnosis, 6 months and 12 months post diagnosis. Associations are reported as p-values with 95% confidence intervals. Predictors with continuous variables were grouped (e.g. Delay from disease onset to diagnosis ≤ 2 months or > 2month, time from diagnosis to inactive disease ≤ 6 months or > 6 months, age at diagnosis and age at first symptoms < 5 years or ≥ 5 years, ESR < 26 mm/h or ≥ 26 mm/h, CRP ≤ 10 mg/L or > 10 mg/L, treatment duration < 6 months or ≥ 6 months for biologic agents, DMARDs and glucocorticoids).

Kaplan-survival curves were created for each disease evolution type (i.e. monophasic, polyphasic and persistent) to assess the cumulative probabilities of attaining inactive disease as well as active joint count 0. Active joint count is defined as either a swelling, or a limitation of the range of motion with pain or tenderness.(2)

Results

Demographics, clinical and laboratory characteristics. 45 patients with a median age of 4.75 years at diagnosis were included. 62% were females. The median delay between symptom onset and diagnosis was four weeks. First description of inactive disease was made after a median period of 18 months. The median follow-up was 5 years. The origin of patients and further demographic characteristics are shown in table 1.

Table 1 Demographics of study cohort

	All	Monophasic	Polyphasic	Persistent
Number of patients	45	12	17	16
Female (%)	62.2	91.7	58.8	43.8
Age at diagnosis in years	4.75 (2.4 – 8.6)	8.87 (5.4 – 13.2)	3.64 (1.6 – 6.5)	4.35 (2.7 – 7.2)
Disease duration at diagnosis in months	1.00 (0 .25-1.75)	1.00 (0 – 3.5)	1.00 (0 – 60)	5.50 (1.0 – 8.0)
Time to follow-up in years	5.02 (3.3 – 8.7)	3.6 (2.7 – 5.0)	5.1 (3.3 – 6.9)	8.7 (4.5 – 10.1)
Country of birth (% of patients)				
France	6.7	8.3	5.9	6.25
Morocco	26.7	0	23.5	50
Portugal	2.2	8.3	0	0
Spain	2.2	0	5.9	0
Suisse	15.6	25	11.7	12.5
Unknown	46.7	58.3	52.9	31.2
Country of follow-up (% of patients)				
Belgium	18	17	18	19
France	24	25	29	19
Morocco	27	0	24	50
Suisse	31	58	29	12
Time to Inactive disease in months	18 (6 – 46)	12 (3.25 – 20.25)	6 (3 – 18)	62.5 (39.25 – 85.25)

Median (25-75 percentiles) if not otherwise specified

Corresponding to their disease evolution, patients were classified in monophasic (n=12; 26.7%), polyphasic (n= 17; 37.8%) or persistent (n=16; 35.6%) disease evolution groups. The persistent disease evolution group showed two particularities concerning demographic features compared to the other disease courses: The time to diagnosis was five times longer and the duration of active disease until the first description of inactive disease was over 5 years in this group.

Initial clinical presentation was characterized by fever for all three disease evolution groups. Other systemic symptoms such as cutaneous rash and splenomegaly were less frequent but showed differences in prevalence between the three evolution groups – rash and organomegaly were more prevalent in the monophasic and polyphasic disease evolution groups than in the persistent group. Serositis, on the other hand, was diagnosed more frequently in the polyphasic (23.5%) and the persistent (12.5%) disease evolution groups, no patient from the monophasic group presented with serositis. Arthritis at diagnosis was seen in all patients from the persistent disease evolution group, and in 75% and 94.1% of the monophasic and the polyphasic patients, respectively. Oligoarthritis during the first 6 months of disease was observed in 58.8% of the polyphasic patients, whereas polyarthritis was found in 75% of the persistent disease evolution patients. During disease course, 87.5% of the patients with persistent disease evolution presented a polyarticular arthritis. Inflammatory laboratory markers, such as Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), varied across disease groups. Median ESR values at diagnosis were the highest in the persistent group with 90 mm/h and the lowest in the monophasic group with 71 mm/h. CRP values were the most elevated in the polyphasic group with 115.5 mg/L followed by the persistent disease evolution category with 100.5 mg/L and were much lower in the monophasic group with 34 mg/L. Median values of ESR and CRP for the whole study population as well as more detailed information on the results including interquartile ranges are shown in table 2.

Table 2 Clinical and laboratory characteristics at diagnosis

Number of patients (%)	All (n = 45)	Monophasic (n=12)	Polyphasic (n=17)	Persistent (n=16)
Fever	44 (97.8%)	12 (100%)	17 (100%)	15 (93.8%)
Rash	30 (65.2%)	9 (75%)	12 (70.6%)	9 (56.3%)
Lymphadenopathy	18 (40%)	4 (33.3%)	7 (41.2%)	7 (43.8%)
Hepatomegaly	8 (17.8%)	2 (16.7%)	3 (17.6%)	3 (18.8%)
Splenomegaly	9 (20%)	4 (33.3%)	3 (17.6%)	2 (12.5%)
Serositis	6 (13.3%)	0 (0%)	4 (23.5%)	2 (12.5%)
Arthralgia	16 (35.5%)	7 (58.3%)	6 (35.3%)	3 (18.8%)
Arthritis at any moment of disease	41 (91.1%)	9 (75%)	16 (94.1%)	16 (100%)
Joint count during first 6 months				
1-4 joints	16 (35.5%)	4 (33.3%)	8 (58.8%)	4 (25%)
5+ joints	23 (51.1%)	4 (33.3%)	7 (41.2%)	12 (75%)
Joint count during disease course (after first 6 months)				
1-4 joints	12 (26.6%)	3 (25%)	7 (41.2%)	2 (12.5%)
5+ joints	26 (57.5%)	4 (33.3%)	8 (58.8)	14 (87.5%)
ESR [mm/h]	77 (40 – 100)	71 (22.7 – 86)	88 (59 – 120)	90 (32 – 109.5)
CRP [mg/L]	90 (23.5 – 120.5)	34 (8 – 87.2)	115.5 (12.5 – 138.5)	100.5 (70.1 – 158.7)

Median (25-75 percentiles) if not otherwise specified

Treatment. All patients were treated with Non-steroidal Anti-inflammatory Drugs (NSAID) and nearly all with glucocorticoids. All children in the polyphasic and persistent groups and 66% of the monophasic group were treated with biologic agents. Biologic agents used in this SoJIA population were Abatacept (CTLA4-Ig), Adalimumab (Anti-TNF-α), Anakinra (Anti-IL 1 receptor-antagonist), Canakinumab (Anti-IL1β antibody), Etanercept (Anti-TNF-α), Rituximab (Anti-CD20 antibody), Tocilizumab (Anti-IL6R antibody). Disease Modifying Anti-Rheumatic Drugs (DMARD) were used in 93.8%, 70.6% and 33.3% of the persistent, the polyphasic and the monophasic patients, respectively. The DMARDs used were Methotrexate and Ciclosporin. Detailed information on the number of patients treated with biologics, glucocorticoids, NSAID and DMARDs as well as information on treatment duration are shown in table 3.

Table 3 Treatment of study cohort

Number of patients (%)	All (n = 45)	Monophasic (n=12)	Polyphasic (n=17)	Persistent (n=16)
Biologics	41 (91.1%)	8 (66.7%)	17 (100%)	16 (100%)
Glucocorticoids	43 (95.6%)	12 (100%)	15 (88.2%)	16 (100%)
NSAID	35 (77.8%)*	7 (58.3%)	13 (76.5%)	15 (93.8%)
DMARD	31 (68.9%)	4 (33.3%)	12 (70.6%)	15 (93.8%)
Median treatment duration in years (range) for patients under:				
Biologics	3.6 (0 – 12.8)	2.2 (0 – 5.4)	3.3 (1.7 – 10.8)	6 (2 – 12.8)
Glucocorticoids	1.4 (0 – 10.1)	0.5 (0.1 – 1.4)	2.2 (0 – 7.6)	2.9 (0.9 – 10.1)
NSAID	0.8 (0 – 10.5)	0.06 (0 – 0.4)	1.1 (0 – 4.3)	2.8 (0 – 10.5)
DMARD	1.1 (0 – 13.2)	0 (0 – 4.2)	1.1 (0 – 11.8)	4.7 (0 – 13.2)

** Not reported in the JIRcohorte for 15 patients*

Differences between monophasic, polyphasic and persistent disease evolution groups. Analyses of variance (ANOVA) was performed for demographic, clinical, laboratory and medication features at diagnosis, 6 months and 12 months. At time point “diagnosis”, significant differences between the three disease evolution groups monophasic, polyphasic and persistent were seen for the female sex (91.7%, 58.8%, 43.8% respectively; $p < 0.05$) and the median age at diagnosis (8.8 years, 3.6 years, 4.3 years respectively; $p < 0.05$). No differences were seen in the initial clinical presentation. At time point “6 months”, significant differences between the three evolution groups (i.e. monophasic, polyphasic and persistent) were seen in the mean value of disease activity evaluated with the Visual Analogue Scale (VAS) by physician (VAS 0.12 cm, 1.1 cm, 5.3 cm; $p < 0.05$) as well as by the patient (VAS 0

cm, 4 cm, 7.2 cm; $p < 0.05$). At time point "12 months", significant differences between the monophasic, polyphasic and persistent group were found in clinical features, such as the mean number of active joints (0.12, 0.6, 4.3 joints; $p < 0.001$), disease activity scored by physician (VAS 0 cm, 1.4 cm, 6.2 cm; $p < 0.001$) as well as by patient (VAS 0 cm, 1.5 cm, 5.9 cm; $p < 0.05$) and in laboratory features such as the mean value of the inflammatory markers ESR (10.6 mm/h, 10.7 mm/h, 47.1 mm/h; respectively; $p < 0.05$) and CRP (1.7 mg/L, 20.5 mg/L, 82.1 mg/L; $p < 0.05$). Complete analysis of variance is shown in table 1, table 2 and table 3 of the annex.

Prediction of a persistent disease evolution. Each predictor was first analyzed by univariate logistic regression comparing persistent disease evolution with non-persistent disease evolution (i.e. monophasic and polyphasic). A delay from disease onset to diagnosis for more than 2 months was significantly more frequent in the persistent evolution group (62.5% vs. 24.1%; $p < 0.05$). There was no significant difference observed for the predictors female sex or age at diagnosis ≥ 5 years. Complete information on demographic features analyzed by univariate logistic regression are shown in table 4.

Table 4 Demographic features of patients with persistent disease evolution vs. non-persistent evolution

% of patients	Persistent disease evolution (n=16)	Non-persistent disease evolution (n=29)
Female Gender	43.8	72.4
Diagnosis confirmed	93.8	93.1
Delay between disease onset and diagnosis > 2 months	62.5*	24.1
Delay between diagnosis and first description of inactive disease > 6 months	100	58.6
Age at diagnosis ≥ 5 years	37.5	55.2

*Univariate logistic regression, *p-value < 0.05; **p-value < 0.01*

Patients with a persistent evolution suffered significantly more frequently from a polyarthritis at 6 months (18.8% vs. 3.4%; $p < 0.05$). At 12 months, persistent patients had significantly higher rates of active arthritis (56.3% vs. 13.8%; $p < 0.01$). The ESR measures were significantly more frequently found to be higher than 26 mm/h in the persistent group at 6 months (31.3% vs. 3.4%; $p < 0.05$). The rate of elevated ESR values as well as elevated CRP values at 12 months were significantly higher in the persistent group (ESR ≥ 26 mm/h: 37.5% vs. 3.4%, $p < 0.01$; CRP > 10 mg/L: 62.5% vs. 13.8%, $p < 0.01$). Detailed results on all clinical features analyzed are shown in table 5.

Table 5 Clinical features of patients with persistent disease evolution vs. non-persistent disease evolution

	Persistent disease evolution (n=16)			Non-persistent disease evolution (n=29)		
% of patients	**Diagnosis**	**6 months**	**12 months**	**Diagnosis**	**6 months**	**12 months**
Arthritis	100	31.3	56.3**	86.2	13.8	13.8
Oligoarthritis	25	12.5	37.5**	41.4	10.3	13.8
Polyarthritis	75	18.8*	18.8	37.9	3.4	0
Not specified	0	0	0	6.9	0	0
Fever	93.8	0	25	100	3.4	0
Rash	56.3	12.5	18.8	72.4	3.4	6.9
Lymphadenopathy	43.8	0	6.3	37.9	3.4	0
Hepatomegaly	18.8	0	0	17.2	0	0
Splenomegaly	12.5	0	0	24.1	0	0
Serositis	12.5	6.3	0	13.8	0	0
ESR ≥ 26 mm/h	68.8	31.3*	37.5**	41.4	3.4	3.4
CRP > 10 mg/L	62.5	12.5	62.5**	48.3	6.9	13.8

*Univariate logistic regression, *p-value < 0.05; **p-value < 0.01*

The treatment frequency with DMARD was significantly higher for the patients with persistent evolution (93.8% vs. 55.2%; $p < 0.05$). DMARD treatment duration of > 6 months was significantly more frequent in the persistent group (93.7% vs 41.4%; $p < 0.05$). More information on treatment features analyzed in the univariate model are shown in table 6.

Table 6 Treatment features of patients with persistent disease evolution vs. non-persistent disease evolution

% of patients	Persistent disease evolution (n=16)	Non-persistent disease evolution (n=29)
Biologic agents	100	86.2
Glucocorticoids	100	93.1
NSAID	93.8	69
DMARD	93.8*	55.2
Biologic treatment duration ≥ 6 months	100	86.2
Glucocorticoid treatment duration ≥ 6 months	100	62
DMARD treatment duration ≥ 6 months	93.7**	41.4

*Univariate logistic regression, *p-value < 0.05; **p-value < 0.01*

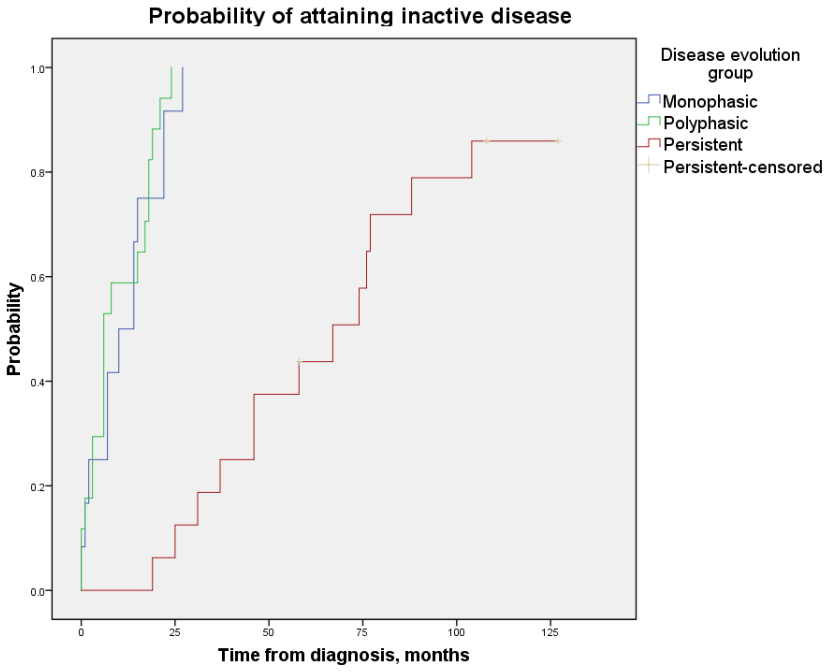
All predictors identified as significant in the univariate model were analyzed together in the multivariate logistic regression analysis. The predictors included were: Delay between disease onset and diagnosis > 2 months, Active joint count ≥ 1 at 6 months, Arthritis at 6 months, ESR ≥ 26 mm/h at 6 months, Active joint count ≥ 1 at 12 months, Arthritis at 12 months, VAS ≥ 1 at 12 months, ESR ≥ 26 mm/h at 12 months, CRP > 10 mg/L at 12 months, DMARD use, DMARD treatment duration ≥ 6 months, NSAID treatment duration ≥ 6 months. No significant differences within the tested variables were found between the persistent disease evolution group compared to the non-persistent disease evolution group. The results of the multivariate logistic regression analysis are shown in the table 4 in the annex.

Disease outcome. The probability of attaining inactive disease at 6 months for the whole study cohort was 26.7%. At 12 months, 50% of the monophasic disease evolution group and 58.8% of the polyphasic disease evolution group achieved inactive disease (while persistent disease is defined by the absence of inactive disease for 24 months). At 72 months, 82.5% of the study cohort achieved inactive disease, 100% of the monophasic and the polyphasic group and only 51% of the patients with persistent disease. Detailed information on the probabilities of attaining inactive disease are shown in Table 7. Survival curves of attaining inactive disease as well as attaining active joint-count=0 (JC0) are shown in figure 1.

Table 7 Cumulative probabilities of attaining inactive disease at 6, 12, 24 and 72 months

		Cumulative probabilities of attaining inactive disease (number of patients still with active disease)			
Disease evolution group	N° patients	6 months	12 months	24 months	72 months
Whole study cohort	45	0.267 (33)	0.356 (29)	0.644 (15)	0.825 (7)
Monophasic	12	0.250 (10)	0.500 (6)	1 (0)	1 (0)
Polyphasic	17	0.529 (8)	0.588 (7)	1 (0)	1 (0)
Persistent	16	0 (16)	0 (16)	0.062 (15)	0.510 (7)

Figure 1 Kaplan-Meier survival curve: probability of attaining inactive disease in three different evolution groups - monophasic, polyphasic, persistent

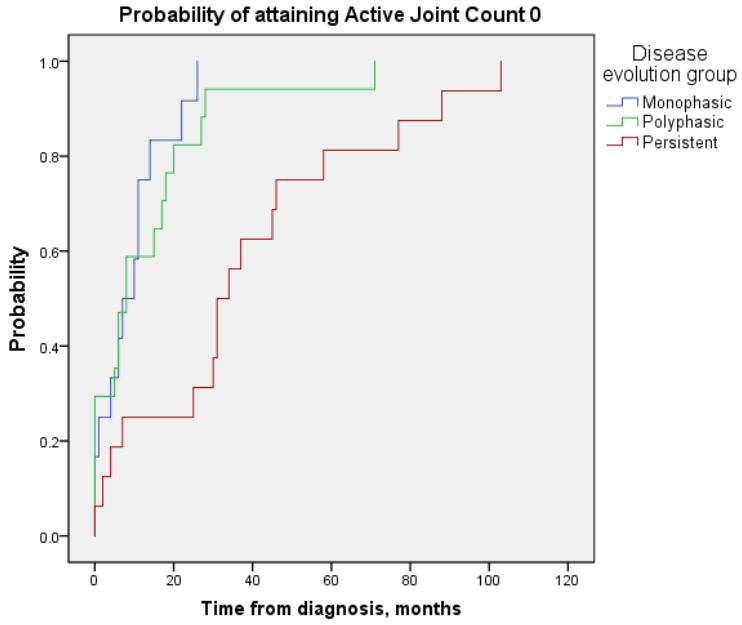


The probability of achieving JC0 at 6 months was 35.6% for the 45 patients included. For the 16 patients of the persistent disease evolution group, 18.7% achieved JC0 at 6 months. At 2 years post diagnosis, the majority in the polyphasic achieved inactive joint count, but 69% of the persistent evolution group still had active arthritis. At the last measured time point, 72 months post diagnosis, all patients of the polyphasic groups had JC0, whereas in the persistent group, nearly 20% of the patients still had JC ≥ 1. Detailed information on the probabilities of attaining JC0 are shown in table 8. Survival curves of attaining active joint-count=0 (JC0) are shown in figure 2.

Table 8 Cumulative probabilities of attaining active joint count = 0 at 6, 12, 24 and 72 months

		Cumulative probabilities of attaining active joint count 0 (number of patients still with joint count ≥ 1)			
Disease evolution group	N° patients	6 months	12 months	24 months	72 months
Whole study cohort	45	0.356 (29)	0.511 (22)	0.644 (15)	0.933 (3)
Monophasic	12	0.417 (7)	0.750 (3)	1 (0)	1 (0)
Polyphasic	17	0.471 (9)	0.588 (7)	0.824 (3)	1 (0)
Persistent	16	0.187 (13)	0.250 (12)	0.312 (11)	0.812 (3)

Figure 2 Kaplan-Meier survival curve: probability of attaining active joint count = 0 in three different evolution groups - monophasic, polyphasic, persistent



Discussion

Systemic-onset juvenile idiopathic arthritis is a chronic disease that can remain active over several years resulting in significant morbidity for young adults, and has an impact on their social, professional and financial future. Although it has been established that there are three different types of disease evolution, information on the predictors of the disease course is limited. The present study was designed to describe the prevalence and clinical course of the different disease evolution types as well as to investigate the prognostic capacity of clinical features to better predict a chronic evolution. Our results validated the existence of the previously described disease evolution types: monophasic, polyphasic and persistent evolution. Over a third of the cohort had a chronic course of disease, that could be classified as persistent. A further third had at least one relapse. These findings, in comparison to a prospective observational study that analyzed 45 patients treated in an academic rheumatology center in Canada between 1996 and 2000, did show a different distribution in disease evolution classifications with nearly half of the children classified in the persistent group and a great minority in the polyphasic group. (26) Such differences between studies remain extremely common due to the absence of a unified definition for inactive disease or remission and therefore classification of disease evolution groups cannot be standardized. For instance, a recent study in an Indian setting found significant differences in the percentage of children classified in each disease evolution category; the authors suggested that it resulted from a divergence in the definition of disease remission (25); moreover, they may also result from the bias of selection because of a non-randomization of the population treated in the different centers included in the studies.

Demographic features, such as age at disease onset, sex and time to follow-up, are consistent with findings in previous studies. (8,25) Most children in this cohort presented initially with fever and/or arthritis. Other systemic symptoms such as cutaneous rash, lymphadenopathies, organomegalies or serositis were less frequent: these results are in agreement with a retrospective observation study that included 136 patients diagnosed with SoJIA from three tertiary rheumatology referral centers in the United States of America between 1990 and 2005. (8)

Strikingly, the results of our study show that a longer delay to diagnosis was associated with a poorer outcome (i.e. a persistent disease evolution). This finding contrasts with the observation by the cohort study of Janow et al., where data on 372 SoJIA patients were collected through convenience sampling between 2010 and 2013 in 62 participating centers of the United States of America and Canada. They observed a shorter delay from symptom onset to diagnosis for patients with a chronic course of disease. (29) This inconsistency may be due to the difference

in the definition of the persistent disease evolution group by the two studies. Janow et al. identified a sub group called *"persistent arthritis only"* where only children with arthritis (i.e. exclusion of patients with systemic symptoms at time point "enrollment") and an active disease over two years were included. Comparison is therefore difficult as in our study, patients with active disease over two years with either elevated laboratory markers, systemic or articular symptoms were classified in the persistent group. To the best of our knowledge, our study is the first to demonstrate a possible association between a longer delay to diagnosis (> 2 months) and the outcome of a persistent disease evolution. In consideration of the framework and limitations of this study (named further below), no theory is known to support this finding and only hypotheses on the possible reasons can be formulated. One hypothesis that may support the finding is known as "the window of opportunity". In this simplified model, the author claims that pro-inflammatory cytokines of the innate immune system (e.g. IL-1β) would activate the "*antigen-driven T-cell immunity*" in a second stage of disease, and thereby promote chronic arthritis by adaptive immunity in this well-known autoinflammatory disease. (30) Therefore, it is thought that early effective intervention is crucial to interrupt the biphasic process and avoid chronic articular disease. A longer period to effective diagnosis may also imply a delay to therapy, "the window of opportunity" could be missed and could thus lead to chronic arthritis. The results of our study may support some elements of this hypothesis by showing important articular involvement in the persistent group at 12 months as well as the risk of having an active joint count ≥1 at 72 months at nearly 20%. One could hypothesis, that on target therapy may not be enough to achieve inactive disease, as an established disease may result from complex immunological pathways and a multitude of cytokines (e.g. IL-1β, IL-6, IL-18, IL-17) implicated in the inflammatory process of SoJIA. Therefore, it may be the high complexity of the aberrant innate immune system in this pathology rendering therapy and prediction of disease evolution difficult, rather than an autoimmune mechanism. (18,31,32)

Our univariate findings, with the significantly higher frequency of arthritis and the significantly higher rate of elevated inflammatory markers during the first year post-diagnosis in the chronic disease evolution group, are tendencies that mirror identified predictors by a multiple regression model in previous studies. (26,33–35) We could not find any significant difference between the persistent and non-persistent groups in the conducted multivariate analysis.

In 2012, Beukelman et al. reported a higher use of Methotrexate and Ciclosporin in SoJIA patients with polyarthritis and children with radiologic damage, respectively. (36) Therefore, an important use of DMARDs in the persistent group of this study could retrospectively be interpreted as an indirect sign of a greater articular involvement. Nonetheless, the interpretation of these results needs to be treated with caution as there was no analysis on

confounding factors done. The long treatment duration in the chronic group is interlinked with the definition of the group but should also be seen as an evidence of how difficult treatment of these chronically affected children is. We also provide evidence that therapeutic strategies remain heterogenous and are based on exacerbation if the initial essay is not effective. Furthermore, we show that glucocorticoids and NSAID remain important baseline therapies, but that biologic agents are faster and more frequently used in the therapeutic procedure due to important scientific evidence of their efficacy and safety in SoJIA. (10,12,37,38)

The probability of attaining inactive disease within the whole study population are consistent with earlier findings of a prospective Canadian cohort study published in 2015. In both studies, two-thirds of the children suffering from SoJIA achieved inactive disease within two years of diagnosis. In the remaining group, a small percentage of patients did not achieve inactive disease throughout the whole study period. (39) An outcome that corresponds with the persistent disease evolution category in this study.

In line with our findings, the ability of a rapid decrease of active joint count during first two years has been reported by Gunzman et al. in 2015. Nonetheless, as most patients achieve active-joint-count=0 by 72 months post-diagnosis, there are some children in the persistent disease evolution group suffering from remaining active joints underlining the severity and long-lasting process of SoJIA creating great morbidity.

One of the limitations of this study is the non-standardized retrospective data collection due to limited time and resources within the framework of this master thesis. Therefore, patients included in this study, despite the complete information on disease activity, had nonetheless missing information on medication use, such as non-reported glucocorticoid or NSAID therapy, missing information on laboratory values as well as missing VAS evaluations by physicians and patients. The missing information complicated the multivariate statistical analysis by excluding an important number of cases. The multivariate model did not show any statistically significant difference between the persistent disease evolution group vs. non-persistent group. Therefore, no effective predictor of a chronic disease evolution was identified. Another limitation is the classification criteria of patients in the polyphasic disease evolution group, who were defined by a relapse of active disease after having achieved inactive disease, making comparison difficult between studies that used different remission criteria.

In conclusion, we have further validated the existence of three clinically discernable disease evolution types in SoJIA, which may be predicted at diagnosis by several clinical and demographic features. Further research should concentrate on standardized definitions of inactive disease and remission, allowing meaningful meta-analysis. Moreover, prospective standardized data collection in multicenter cohort studies are needed to generate enough statistical power to confirm or reject the presented tendencies within this study.

Bibliography

1. Still GF. On a Form of Chronic Joint Disease in Children. Medico-Chir Trans [Internet]. 1897 [cited 2017 Sep 21];80:47-60.9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2036674/

2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol [Internet]. 2004 Feb 1 [cited 2017 Mar 2];31(2):390–2. Available from: http://www.jrheum.org/content/31/2/390

3. Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun [Internet]. 2012 Jun [cited 2017 May 25];13(4):289–98. Available from: https://www.nature.com/gene/journal/v13/n4/full/gene20123a.html

4. Davies R, Southwood T, Kearsley-Fleet L, Lunt M, Baildam E, Beresford MW, et al. Mortality rates are increased in patients with systemic juvenile idiopathic arthritis. Arch Dis Child [Internet]. 2017 Feb 1 [cited 2017 Oct 24];102(2):206–7. Available from: http://adc.bmj.com/content/102/2/206.2

5. Ravelli A, Martini A. Juvenile idiopathic arthritis. The Lancet [Internet]. 2007 Mar 3 [cited 2017 Sep 13];369(9563):767–78. Available from: http://www.sciencedirect.com/science/article/pii/S0140673607603638

6. Hinze CH, Holzinger D, Lainka E, Haas J-P, Speth F, Kallinich T, et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J [Internet]. 2018 Jan 22 [cited 2018 Oct 30];16. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778670/

7. Hofer MF, Mouy R, Prieur AM. Juvenile idiopathic arthritides evaluated prospectively in a single center according to the Durban criteria. J Rheumatol [Internet]. 2001 May 1 [cited 2017 Mar 2];28(5):1083–90. Available from: http://www.jrheum.org/content/28/5/1083

8. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, Arkachaisri T, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). J Rheumatol. 2008 Feb 1;35(2):343–8.

9. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med. 2005 May 2;201(9):1479–86.

10. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 Dec 20;367(25):2396–406.

11. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011 May 1;70(5):747–54.

12. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 Dec 20;367(25):2385–95.

13. Bielak M, Husmann E, Weyandt N, Haas J-P, Hügle B, Horneff G, et al. IL-6 blockade in systemic juvenile idiopathic arthritis – achievement of inactive disease and remission (data from the German AID-registry). Pediatr Rheumatol Online J [Internet]. 2018 Apr 5 [cited 2018 Oct 30];16. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5887199/

14. Lotito APN, Campa A, Silva CAA, Kiss MHB, Mello SBV. Interleukin 18 as a marker of disease activity and severity in patients with juvenile idiopathic arthritis. J Rheumatol. 2007 Apr 1;34(4):823–30.

15. Weiss ES, Girard-Guyonvarc'h C, Holzinger D, de Jesus AA, Tariq Z, Picarsic J, et al. Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome. Blood. 2018 Mar 29;131(13):1442–55.

16. Imbrechts M, Avau A, Vandenhaute J, Malengier-Devlies B, Put K, Mitera T, et al. Insufficient IL-10 Production as a Mechanism Underlying the Pathogenesis of Systemic Juvenile Idiopathic Arthritis. J Immunol. 2018 Nov 1;201(9):2654–63.

17. Avau A, Put K, Wouters CH, Matthys P. Cytokine balance and cytokine-driven natural killer cell dysfunction in systemic juvenile idiopathic arthritis. Cytokine Growth Factor Rev. 2015 Feb;26(1):35–45.

18. Bruck N, Schnabel A, Hedrich CM. Current understanding of the pathophysiology of systemic juvenile idiopathic arthritis (sJIA) and target-directed therapeutic approaches. Clin Immunol. 2015 Jul;159(1):72–83.

19. Vastert SJ, Kuis W, Grom AA. Systemic JIA: New Developments in the Understanding of the Pathophysiology and Therapy. Best Pract Res Clin Rheumatol. 2009 Oct;23(5):655–64.

20. Gabay C, Fautrel B, Rech J, Spertini F, Feist E, Kötter I, et al. Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease. Ann Rheum Dis. 2018 Jun;77(6):840–7.

21. Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JMP, Cohen N, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatol Oxf Engl. 2016 Apr;55(4):669–79.

22. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. Arthritis Res Ther [Internet]. 2017 [cited 2018 Oct 5];19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5700562/

23. Spiegel LR, Schneider R, Lang BA, Birdi N, Silverman ED, Laxer RM, et al. Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: A multicenter cohort study. Arthritis Rheum [Internet]. 2000 Nov 1 [cited 2017 May 25];43(11):2402–9. Available from: http://onlinelibrary.wiley.com/doi/10.1002/1529-0131(200011)43:11<2402::AID-ANR5>3.0.CO;2-C/abstract

24. Lomater C, Gerloni V, Gattinara M, Mazzotti J, Cimaz R, Fantini F. Systemic onset juvenile idiopathic arthritis: a retrospective study of 80 consecutive patients followed for 10 years. J Rheumatol [Internet]. 2000 Feb [cited 2017 Oct 24];27(2):491–6. Available from: http://europepmc.org/abstract/med/10685819

25. Dewoolkar M, Cimaz R, Chickermane PR, Khubchandani RP. Course, Outcome and Complications in Children with Systemic Onset Juvenile Idiopathic Arthritis. Indian J Pediatr [Internet]. 2017 Feb 23 [cited 2017 Mar 12];1–5. Available from: https://link.springer.com/article/10.1007/s12098-017-2293-5

26. Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: Significance of early clinical and laboratory features. Arthritis Rheum. 2006 May 1;54(5):1595–601.

27. Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N, Childhood Arthritis Rheumatology Research Alliance (CARRA), et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res [Internet]. 2011 Jul 1 [cited 2017 May 20];63(7):929–36. Available from: http://onlinelibrary.wiley.com/doi/10.1002/acr.20497/abstract

28. Wallace CA, Ruperto N, Giannini E, Alliance CA and RR, Organization PRIT, Group PRCS. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol [Internet]. 2004 Nov 1 [cited 2017 May 20];31(11):2290–4. Available from: http://www.jrheum.org/content/31/11/2290

29. Janow G, Schanberg LE, Setoguchi S, Hasselblad V, Mellins ED, Schneider R, et al. The Systemic Juvenile Idiopathic Arthritis Cohort of the Childhood Arthritis and Rheumatology Research Alliance Registry: 2010-2013. J Rheumatol. 2016 Sep 1;43(9):1755–62.

30. Nigrovic PA. Review: Is There a Window of Opportunity for Treatment of Systemic Juvenile Idiopathic Arthritis? Arthritis Rheumatol. 2014 Jun 1;66(6):1405–13.

31. Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Sève P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. Immunol Res. 2015 Feb 1;61(1):53–62.

32. Gattorno M, Piccini A, Lasigliè D, Tassi S, Brisca G, Carta S, et al. The pattern of response to anti–interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2008 May 1;58(5):1505–15.

33. Woo P. Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome. Nat Rev Rheumatol [Internet]. 2006 [cited 2017 Oct 24];2. Available from: http://www.readcube.com/articles/10.1038/ncprheum0084

34. Lomater C, Gerloni V, Gattinara M, Mazzotti J, Cimaz R, Fantini F. Systemic onset juvenile idiopathic arthritis: a retrospective study of 80 consecutive patients followed for 10 years. J Rheumatol. 2000 Feb;27(2):491–6.

35. Dewoolkar M, Cimaz R, Chickermane PR, Khubchandani RP. Course, Outcome and Complications in Children with Systemic Onset Juvenile Idiopathic Arthritis. Indian J Pediatr. 2017 Feb 23;1–5.

36. Beukelman T, Ringold S, Davis TE, DeWitt EM, Pelajo CF, Weiss PF, et al. Disease Modifying Anti-Rheumatic Drug Use in the Treatment of Juvenile Idiopathic Arthritis: A Cross-Sectional Analysis of the CARRA Registry. J Rheumatol. 2012 Sep;39(9):1867–74.

37. Klotsche J, Raab A, Niewerth M, Sengler C, Ganser G, Kallinich T, et al. Outcome and Trends in Treatment of Systemic Juvenile Idiopathic Arthritis in the German National Pediatric Rheumatologic Database, 2000–2013. Arthritis Rheumatol. 2016 Dec 1;68(12):3023–34.

38. Otten MH, Anink J, Prince FHM, Twilt M, Vastert SJ, Cate R ten, et al. Trends in prescription of biological agents and outcomes of juvenile idiopathic arthritis: results of the Dutch national Arthritis and Biologics in Children Register. Ann Rheum Dis. 2015 Jul 1;74(7):1379–86.

39. Guzman J, Oen K, Tucker LB, Huber AM, Shiff N, Boire G, et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis. 2015 Oct 1;74(10):1854–60.

Annex

Table 1 of the annex: Analysis of variance (ANOVA): Variables at time point "diagnosis" (Groups = Monophasic, polyphasic, persistent)

		Sum of Squares	df	Mean Square	F	Sig.
Gender	Between Groups	1.606	2	.803	3.759	.031
	Within Groups	8.972	42	.214		
	Total	10.578	44			
Age (diagnosis)	Between Groups	149.556	2	74.778	4.741	.014
	Within Groups	662.420	42	15.772		
	Total	811.976	44			
Age (first symptoms)	Between Groups	188.350	2	94.175	7.366	.002
	Within Groups	536.940	42	12.784		
	Total	725.290	44			
Delay between disease onset and diagnosis (months)	Between Groups	455.037	2	227.519	1.106	.340
	Within Groups	8642.163	42	205.766		
	Total	9097.200	44			
Time from diagnosis to inactive disease (months)	Between Groups	30426.671	2	15213.336	38.781	.000
	Within Groups	16476.129	42	392.289		
	Total	46902.800	44			
ESR (mm/h)	Between Groups	43120.382	2	21560.191	.501	.612
	Within Groups	1031877.026	24	42994.876		
	Total	1074997.407	26			
CRP (mg/L)	Between Groups	22757.950	2	11378.975	2.173	.133
	Within Groups	141377.705	27	5236.211		
	Total	164135.655	29			
Arthritis at any moment of the disease	Between Groups	.218	2	.109	1.733	.189
	Within Groups	2.578	41	.063		
	Total	2.795	43			
Joint count during first 6 months	Between Groups	.439	2	.219	.588	.560
	Within Groups	14.538	39	.373		
	Total	14.976	41			
Joint count during disease course	Between Groups	.636	2	.318	.975	.387
	Within Groups	12.389	38	.326		
	Total	13.024	40			
Enthesitis pain	Between Groups	.000	2	.000	.	.
	Within Groups	.000	34	.000		
	Total	.000	36			
Arthralgia	Between Groups	.975	2	.488	2.024	.149
	Within Groups	7.710	32	.241		
	Total	8.686	34			
Systemic features	Between Groups	.040	2	.020	.902	.413
	Within Groups	.938	42	.022		
	Total	.978	44			
Fever	Between Groups	.040	2	.020	.902	.413
	Within Groups	.938	42	.022		
	Total	.978	44			
Rash	Between Groups	.283	2	.142	.612	.547
	Within Groups	9.717	42	.231		
	Total	10.000	44			
Lymphadenopathy	Between Groups	.036	2	.018	.069	.933
	Within Groups	10.601	41	.259		
	Total	10.636	43			
Hepatomegaly	Between Groups	.004	2	.002	.012	.988
	Within Groups	6.542	41	.160		
Splenomegaly	Between Groups	.313	2	.156	.954	.394
	Within Groups	6.887	42	.164		
	Total	7.200	44			
Serositis	Between Groups	.391	2	.196	1.708	.194
	Within Groups	4.809	42	.114		
	Total	5.200	44			

Table 2 of the annex: Analysis of variance (ANOVA): Variables at time point "6 months" (Groups = Monophasic, polyphasic, persistent)

		Sum of Squares	df	Mean Square	F	Sig.
Fever	Between Groups	.045	2	.023	.475	.629
	Within Groups	.909	19	.048		
	Total	.955	21			
Rash	Between Groups	.321	2	.161	1.705	.202
	Within Groups	2.357	25	.094		
	Total	2.679	27			
Polyadenopathy	Between Groups	.045	2	.022	.563	.577
	Within Groups	.917	23	.040		
	Total	.962	25			
Hepatomegaly	Between Groups	.000	2	.000	.	.
	Within Groups	.000	25	.000		
	Total	.000	27			
Splenomegaly	Between Groups	.000	2	.000	.	.
	Within Groups	.000	25	.000		
	Total	.000	27			
Serositis	Between Groups	.117	2	.058	1.190	.328
	Within Groups	.833	17	.049		
	Total	.950	19			
Number of active joints	Between Groups	30.409	2	15.205	1.279	.297
	Within Groups	285.220	24	11.884		
	Total	315.630	26			
Disease activity VAS by physician	Between Groups	70.729	2	35.365	5.081	.021
	Within Groups	104.396	15	6.960		
	Total	175.125	17			
ESR (mm/h)	Between Groups	1606.617	2	803.308	1.301	.298
	Within Groups	10500.333	17	617.667		
	Total	12106.950	19			
CRP (mg/L)	Between Groups	3721.354	2	1860.677	.915	.418
	Within Groups	38655.704	19	2034.511		
	Total	42377.058	21			

Table 3 of the annex: Analysis of variance (ANOVA): Variables at time point "12 months" (Groups = Monophasic, polyphasic, persistent)

		Sum of Squares	df	Mean Square	F	Sig.
Fever	Between Groups	.679	2	.340	3.188	.058
	Within Groups	2.769	26	.107		
	Total	3.448	28			
Rash	Between Groups	.268	2	.134	1.182	.318
	Within Groups	4.090	36	.114		
	Total	4.359	38			
Polyadenopathy	Between Groups	.044	2	.022	.813	.452
	Within Groups	.929	34	.027		
	Total	.973	36			
Hepatomegaly	Between Groups	.000	2	.000	.	.
	Within Groups	.000	35	.000		
	Total	.000	37			
Splenomegaly	Between Groups	.000	2	.000	.	.
	Within Groups	.000	35	.000		
	Total	.000	37			
Serositis	Between Groups	.000	2	.000	.	.
	Within Groups	.000	27	.000		
	Total	.000	29			
Number of active joints	Between Groups	113.030	2	56.515	11.940	.000
	Within Groups	146.735	31	4.733		
	Total	259.765	33			
Disease activity VAS by physician	Between Groups	160.222	2	80.111	18.679	.000
	Within Groups	85.778	20	4.289		
	Total	246.000	22			
ESR (mm/h)	Between Groups	8339.744	2	4169.872	5.048	.015
	Within Groups	19826.331	24	826.097		
	Total	28166.074	26			
CRP (mg/L)	Between Groups	36828.041	2	18414.020	6.727	.004
	Within Groups	79376.929	29	2737.135		
	Total	116204.970	31			

Table 4 of the annex: multivariate logistic regression analysis

Multivariate logistic regression analysis

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Delay between disease onset and diagnosis > 2 months	17.813	10611.307	.000	1	.999	54477052.250	.000	.
Arthritis at 6 months	-46.639	29100.265	.000	1	.999	.000	.000	.
Oligoarthritis	45.416	16305.213	.000	1	.998	52971699670000000000.000	.000	.
ESR > = 26 mm/h at 6 months	105.561	17881.534	.000	1	.995	6.993E+45	.000	.
Arthritis at 12 months	19.557	15886.598	.000	1	.999	311380998.000	.000	.
VAS patient >= 1 at 12 months	-57.109	10386.744	.000	1	.996	.000	.000	.
ESR > = 26 mm/h at 12 months	-16.031	28626.424	.000	1	1.000	.000	.000	.
CRP > 10 mg/L at 12 months	-2.515	8244.323	.000	1	1.000	.081	.000	.
Disease Modifying Anti-Rheumatic Drugs	-71.620	25244.106	.000	1	.998	.000	.000	.
DMARD treatment duration ≥6 months	154.794	28006.736	.000	1	.996	1.684E+67	.000	.
NSAID treatment duration ≥6 months	12.007	11451.269	.000	1	.999	163898.151	.000	.
Constant	-36.256	10622.710	.000	1	.997	.000		

a. Variable(s) entered on step 1: Delay between disease onset and diagnosis > 2 months, Active joint count >= 1 at 6 months , Arthritis (Oligo- or Polyarthritis) at 6 months, ESR > = 26 mm/h at 6 months, Active joint count >= 1 at 12 months, Arthritis (Oligo- or Polyarthritis) at 12 months, VAS patient >= 1 at 12 months, ESR > = 26 mm/h at 12 months, CRP > 10 mg/L at 12 months, Disease Modifying Anti-Rheumatic Drugs, DMARD treatment duration ≥6 months, NSAID treatment duration ≥6 months.

b. B = Intercept; S.E. = Standard Error; Wald = Wald Chi-Square test; df.: degree of freedom of the Wald Chi-Square test; Sig. = Significance of the Wald Chi-Square test ($p < 0.05$); Exp(B) = Odds Ratio; C.I. for Exp(B) = Confidence Interval