Clinical predictors of remission in systemic juvenile idiopathic arthritis/Still's disease: insight from real-life data and the potential relevance of the 'window of opportunity'

S. Abu-Rumeileh[1], M.V. Mastrolia[2,3], A. Laurent[4], M. Fouillet-Desjonqueres[4], F. Zekre[4], I. Pagnini[2], E. Marrani[2], I. Maccora[2,3], A. Belot[4], G. Simonini[2,3]

[1]Rheumatology Unit, Paediatric Department, AOU Pisana, Santa Chiara Hospital, Pisa, Italy; [2]Rheumatology Unit, ERN ReCONNET Center, Meyer Children's Hospital IRCCS, Florence, Italy; [3]NEUROFARBA Department, University of Florence, Florence, Italy; [4]Nephrology and Rheumatology Unit, Hospices Civils de Lyon, Hôpital Femme-Mère-Enfant, Lyon, France.

Abstract

Objective

To investigate potential predictors of remission and relapse in systemic juvenile idiopathic arthritis (sJIA), in a real-life clinical setting.

Methods

An observational bicentric cohort study was conducted including patients diagnosed with sJIA between 2017 and 2022 in two tertiary paediatric hospitals.

Results

64 sJIA patients were included. The time from first symptom to diagnosis (hazard ratio (HR): 0.991) and interleukin 1 (IL1) inhibitors treatment failure (HR: 0.236) resulted predictors of a longer time to achieve remission on therapy. Clinical inactive disease at month 3 (HR: 3.506) predicted a shorter interval of time to remission off medication while anti-IL1 failure (HR: 0.153) was found to be a predictor of longer time to achieve remission off medication. The presence of rash three months after onset (HR: 5.763) resulted significantly associated with a shorter time to relapse, while the male gender resulted a protective factor (HR: 0.247). IL1 inhibitors non-responder patients (15/42, 35.7%) presented a lower age (p=0.040) and a higher frequency of polyarthritis at onset (p=0.029), a non-monophasic disease course (p<0.001), a higher number of relapses (p=0.010), and a longer time to achieve remission on therapy (p<0.001).

Conclusion

A diagnostic and therapeutic delay predicts a longer time to reach remission in sJIA patients, and seems to affect the response to IL1 inhibition, according to the 'window of opportunity' hypothesis in sJIA treatment. A failure to IL1 inhibitors predicts a longer time to reach remission both on and off medications and is associated with an early polyarticular onset and non-monophasic disease course.

Key words

paediatric rheumatology, systemic juvenile idiopathic arthritis, biological treatment, interleukin-1, predictors of disease clinical course

Sarah Abu-Rumeileh, MD
Maria-Vincenza Mastrolia, MD
Audrey Laurent, MD
Marine Fouillet-Desjonqueres, MD
Franck Zekre, MD
Ilaria Pagnini, MD
Edoardo Marrani, MD
Ilaria Maccora, MD
*Alexandre Belot, MD**
*Gabriele Simonini, MD**

**Contributed equally.*

Please address correspondence to
Sarah Abu-Rumeileh
U.O. di Reumatologia Pediatrica,
Azienda Ospedaliero Universitaria Pisana,
via Roma 67,
56126 Pisa, Italy.
E-mail: sarah.arumeileh@gmail.com

Received on January 16, 2025; accepted in revised form on June 9, 2025.

Funding: this study was supported in part by funds from the 'Current Research Annual Funding' of the Italian Ministry of Health

Competing interests: none declared.

Introduction

Among the various subtypes of juvenile idiopathic arthritis (JIA), systemic JIA (sJIA) / Still's disease, stands out as a distinct clinical entity because of its peculiar pathogenesis attributable to the spectrum of autoinflammatory disorders. It is widely recognised that sJIA represents the most severe type of arthritis in childhood accounting for a non-negligible morbidity and mortality rate.

The disease course may display a significant variability and a profound impact on the disease's natural history was reported after the advent of biological treatment (1). However, the evidence about the role of epidemiological and clinical factors as predictors of different disease trajectories in sJIA patients remains limited, especially because most studies dated back to the pre-biological era (2).

One of the most intriguing theories attempting to explain the pathophysiology of the sJIA clinical course is Nigrovic's biphasic model (3). According to this model, at sJIA onset, there is a dysregulated production of interleukin (IL)-1 within the framework of an innate immune response, underlying systemic inflammatory syndrome and early arthritis. Prolonged aberrant production of IL-1 may promote the development of a pathological T-cell-mediated response that sustains arthritis independently, or at least with reduced susceptibility to IL-1 and its inhibition. Therefore, the early inhibition of IL-1, during what is referred to in this paper as the 'window of opportunity', could prevent the development of a chronic persistent disease course. The opportunity to predict treatment response and the time to achieve remission is a crucial tool for optimising care, enabling a therapeutic approach tailored to the stratification of patients' risk factors.

The main objective of this study is to investigate the presence of potential predictors of an earlier time to relapse and to remission both on and off therapy in sJIA children in a real-life clinical setting. Furthermore, we aimed to compare the demographic and clinical features of IL1 inhibitor responders and non-responders.

Methods

An observational retrospective bicentric cohort study was conducted including patients diagnosed with sJIA according to ILAR criteria (4) and/or PRINTO 2019 provisional criteria (5) between January 2017 and December 2022 belonging to the Rheumatology Unit of Meyer Children's Hospital IRCCS (Florence, Italy) and the Rheumatology Unit of Hospice Civile de Lyon (France). Since it is well known that arthritis may not be present at sJIA onset, this cohort also included subjects in whom this clinical manifestation was absent at sJIA onset (5-8). In such cases, all patients fulfilled the PRINTO 2019 criteria and were previously subjected to genetic testing to exclude monogenic autoinflammatory diseases. Paper and/or electronic medical records were reviewed for data collection. Patients with a follow-up duration of less than one year were excluded.

Demographic, clinical, and laboratory data, recorded through a standardised report form, were collected at the time of diagnosis and after 3 and 6 months, respectively. Any changes or withdrawals in therapy were recorded until the last available follow-up.

Clinically active disease is defined by the presence of systemic symptoms (fever, rash, serositis, organomegaly, or generalised lymphadenopathy) and/or active arthritis, and/or abnormal laboratory tests (elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC) count, in the absence of other concurrent clinical reasons). Clinically inactive disease (CID) is defined by the absence of the above-mentioned clinical features and laboratory abnormalities. A disease flare is defined as the reoccurrence of clinically active disease after a period of inactive disease off medication. Remission is defined after 6 months of clinically inactive disease while still receiving treatment (remission on medications) or after the withdrawal of any medication for at least 3 months (remission off medications). Physician's Global Assessment (PGA) was not systematically available due to the retrospective nature of the study, hence not included in the remission definition.

Table I. Demographic and clinical characteristics at onset of sJIA patients.

Characteristics		All patients, n (%), or median (IQR)	Monophasic n (%), or median (IQR)	Non-Monophasic n (%), or median (IQR)	*p*-value
n. patients		64	37 (57.8%)	27 (42.8%)	-
French nationality		47 (73.4%)	27 (73%)	20 (74.1%)	0.922
Female subjects		30 (46.9%)	13 (35.1%)	17 (63%)	0.028*
Age At diagnosis		6.5 (3-12)	7 (3-12.5)	5 (2-9)	0.075
Time from first symptom to diagnosis, days		23 (14-32.5)	20 (14-28.5)	25 (13-54)	0.384
Length of stay, days		11 (5-14.8)	11 (4-15)	11.5 (6.5-14.75)	0.583
Clinical features at diagnosis	Fever	64 (100%)	37 (100%)	27 (100%)	-
	Fever duration, days	19 (12-26)	19 (11.25-27.7)	19 (13.5-23.5)	0.763
	Typical rash	45 (70.3%)	24 (64.9%)	21 (77.8%)	0.264
	Lymphadenopathy	13 (20.3%)	8 (21.6%)	5 (18.5%)	0.761
	Hepatomegaly	13 (20.3%)	11 (29.7%)	5 (18.5%)	0.306
	Splenomegaly	16 (25%)	8 (21.6%)	5 (18.5%)	0.761
	Arthralgia	53 (82.8%)	32 (86.5%)	21 (77.8%)	0.362
	Arthritis	31 (48.4%)	18 (48.6%)	13 (48.1%)	0.968
	n. of active joints	0.5 (0-3.75)	1 (0-3)	0 (0-5	0.822
	Polyarticular	13 (20.3%)	6 (16.2%)	7 (25.9%)	0.365
	Pharyngodynia	10 (15.6%)	6 (16.2%)	4 (14.8%)	1.00
	Pericarditis	8 (12.5%)	3 (8.1%)	5 (18.5%)	0.268
	Pleurisy	3 (4.7%)	1 (2.7%)	2 (7.4%)	0.568
	MAS	9 (14.1%)	4 (10.8%)	5 (18.5%)	0.475
	Lung involvement	0 (0%)	0 (0%)	0 (0%)	-

SJIA: systemic juvenile idiopathic arthritis, MAS: macrophagic activation syndrome.

A monophasic disease course is defined by a single episode of disease (systemic symptoms with/without arthritis) followed by remission on or off medication without relapses for at least 1 year. The failure of IL-1 inhibitor therapy is defined as the persistence of clinically active disease on anti-IL1 therapy, requiring a switch or addition of therapy. Macrophage activation syndrome (MAS) was defined buy the fulfillment of the 2016 MAS in sJIA criteria proposed by Ravelli *et al*. (9). All the included data were acquired through routine clinical activities and assessed anonymously and retrospectively.

Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were reported as absolute frequencies and percentages (%). The Chi-Square test was adopted to compare categorical variables. Data distribution was assessed by the Shapiro-Wilk test. Non-parametric tests (the Kruskal-Wallis test and the Mann-Whitney U-test) were used as the analysed data resulted in a non-Gaussian distribution.

Cox regression analyses were used to test the eventual associations between sJIA relapse and remission and the continuous and/or categorical variables. Before performing the analysis, each laboratory value was naturally log-transformed to fulfill the normal distribution. For the analyses of prognostic factors, the interval in months from diagnosis to relapse/remission or the date of the last follow-up (March 2023), whichever came first, was calculated. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The assumption of proportional hazard was assessed by Schoenfeld residuals. Statistical significance was considered at *p*-value 0.05. Statistical analyses were carried out with IBM SPSS Statistics v. 21 (IBM Inc., Armonk, USA).

Results

Sixty-four sJIA patients (47/64 from Lyon, 17/64 from Florence) were included during a 6-year study period. Patients' demographic and clinical features at onset are summarised in Table I. A monophasic course was observed in 57.8% of cases (37/64). Regarding gender distribution, 46.9% of patients (30/64) were females. The median age at diagnosis was 6.5 years (IQR 3-12), with a median time from symptom onset to the diagnosis of 23 days (IQR 14–32.5). MAS was diagnosed in 14.1% (9/64) of children at sJIA onset.

Data about the type and timing of treatment are detailed in Table II. Oral glucocorticoids were administered in 70.3% (45/64) of cases while 51.6% (33/64) of patients received intravenous (IV) glucocorticoids; 28.1% (18/64) of patients received steroid therapy for more than 6 months. Anti-IL1 drugs were extensively used, 64.1% (41/64) and 31.25% (20/64) of children received anakinra and canakinumab, respectively.

Almost all patients in our cohort who received a biologic DMARD as initial treatment were treated with anakinra, as anti-IL-1 drugs are readily accessible in both Italy and France, and the treatment regimens currently adopted in the two included centres are similar. Anakinra was administered at disease onset in 40.6% of patients (26/64), while tocilizumab was used in 1.6% (1/64). Conversely, patients who did not respond to IL-1 antagonist therapy were subsequently treated with other biologic drugs, primarily tocilizumab.

The median follow-up period was 22 months (IQR 12–38.8). At the last available follow-up, 93.7% of patients (60/64) achieved remission on medication during the study period and 35/64 (54.7%) sJIA patients obtained a remission off medication. Relapses occurred in 12 cases (18.7%). Sixteen out of 64

Table II. Treatment of sJIA patients.

Treatment	Diagnosis, n (%)	Month 3, n (%)	Month 6, n (%)	Anytime, n (%)
NSAIDs	45 (70.3%)	9 (14.1%)	3 (4.7%)	47 (73.4%)
Oral GC	44 (68.75%)	31 (48.4%)	18 (28.1%)	45 (70.3%)
IV GC	23 (35,9%)	5 (7.8%)	1 (1.6%)	33 (51.6%)
Anakinra	26 (40.6%)	25 (39.1%)	14 (21.9%)	41 (64.1%)
Canakinumab	0 (0%)	9 (14.1%)	12 (18.7%)	20 (31.25%)
Anti-IL1 without GC	7 (10.9%)	15 (23.4%)	17 (26.6%)	-
Tocilizumab	1 (1.6%)	5 (7.8%)	12 (18.7%)	20 (31.25%)
Cyclosporine	2 (3.1%)	3 (4.7%)	4 (6.25%)	7 (10.9%)
Methotrexate	1 (1.6%)	4 (6.25%)	3 (4.7%)	12 (18.7%)
Rituximab	0 (0%)	0 (0%)	0 (0%)	2 (3.1%)
Anti-TNFalpha	0 (0%)	0 (0%)	0 (0%)	2 (3.1%)
Jak-inhibitors	0 (0%)	0 (0%)	1 (1.6%)	3 (4.7%)
MAS825 (anti-IL-1β/IL-18)	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)
IVIg	10 (15.6%)	0 (0%)	0 (0%)	10 (15.6%)
No medication	1 (1.6%)	7 (10.9%)	15 (23.4%)	-

NSAIDs: non-steroidal anti-inflammatory drugs; GC: glucocorticoid; IL: interleukin; IVIg: intravenous immunoglobulin.

(25%) patients experienced complications: MAS was reported in 13/16, 20.3% out of the entire cohort; 3 patients reported drug-induced adverse events (one local skin reaction to anakinra and two allergic reactions to tocilizumab), without opportunistic infections observed over the whole follow-up period. No deaths were reported. At the last available follow-up, no patient exhibited findings related to a potential lung involvement.

At univariate Cox regression analyses, the persistence of skin rash at month 3 (hazard ratio (HR) and 95% confidence interval (95% CI): 0.468 (0.255–0.860), p=0.014), a longer interval from first symptom to diagnosis (HR (95% CI): 0.992 (0.985–0.999), p=0.035) and a failure to anti-IL1 treatment (HR (95% CI): 0.368 (0.188–0.720), p=0.004) were reported as negative prognostic factors for time to remission on medication, while the achievement of a CID at month 3 was observed to be a positive prognostic factor (HR (95% CI): 2.259 (1.323–3.857), p=0.003)) (Table III).

A longer time from the first symptom to diagnosis (HR (95% CI): 0.991 (0.984–0.999), p=0.021) and anti-IL1 treatment failure (HR (95% CI): 0.236 (0.158–0.672), p=0.002) maintained a significant predictive role at the multivariate Cox analyses.

Similarly, CID at month 3 (HR (95% CI): 3.506 (1.045–11.760), p=0.042) predicted a shorter interval of time to remission off medication while anti-IL1 failure (HR (95% CI): 0.153 (0.035–0.661), p=0.012) was found to be a predictor of longer time to achieve remission off medication at multivariate Cox analyses (Table III).

At univariate Cox regression analysis, rash at month 3 (HR (95% CI): 5.847 (1.899–18.000), p=0.002) and anti-IL1 treatment failure (HR (95% CI): 3.081 (1.035–9.176), p=0.043) resulted significantly associated with an earlier relapse, while male gender resulted protective, determining a longer time to relapse (HR (95% CI): 0.229 (0.063–0.834), p=0.025). At multivariate Cox analyses, male gender (HR (95% CI): 0.247 (0.66-0.933), p=0.039) and rash at month 3 (HR (95% CI): 5.763 (1.796–18.498), p=0.003) confirmed a trend towards an association with time to relapse (Table III).

As regards patients treated with anti-IL1 agents (42/64), 27/42 (64.3%) were considered as responders and 15/42 (35.7%) as non-responders (Table IV). Non-responders exhibited a lower age at onset (median of 3 years, p=0.040) and a higher frequency of polyarthritis (p=0.029). Furthermore, a statistically significant association between non-response to anti-IL1 and steroid administration at 3 months (p=0.044) and at 6 months (p<0.001) after sJIA diagnosis was observed. Treatment failure was also associated with a non-monophasic course (p<0.001), a higher number of relapses (p=0.010), a lower remission rate on (p=0.085) and off (p=0.008) medication, and a longer time to achieve remission on treatment (p<0.001). Of note, non-responders reported a longer time interval in starting anti-IL1 treatment (median 56 days *vs*. 27 days), although this result did not reach a statistically significant (p=0.098) value.

Among the non-responder patients, 12/15 achieved remission with the therapeutic switch to tocilizumab (in 3 cases in combination with methotrexate), while 1 patient achieved remission switching to ruxolitinib and one to MAS825 (anti-IL-1β/IL-18). Finally, it was necessary to reintroduce steroid therapy for one patient due to the occurrence of two relapses during anti-IL-1 treatment.

Discussion

We assessed 64 consecutive sJIA patients from two tertiary referral Paediatric Rheumatology centres. Within our cohort, non-monophasic forms accounted for 42.2%, while the majority of patients experienced a monophasic disease course. The prevalence of non-monophasic forms is slightly lower compared to previously reported rates, ranging from 48% to over 50% (2, 9-12). Nevertheless, our findings result in agreement with the observations by Baris *et al*., who demonstrated that the proportion of monophasic disease appears to be increasing after 2004. This trend could be attributed to a more precocious diagnosis and the adoption of a more aggressive treatment with biologic disease-modifying anti-rheumatic drugs (bDMARDs) in recent years (13).

Demographic features, such as gender and age at onset, are consistent with previous studies (2, 14). Age has not been identified as a significant predictor of time to relapse or remission. However, in our cohort, anti-IL1 non-responder patients exhibited a lower age at onset (median of 3 years). A study by Russo *et al*. reported that very early onset sJIA (<18 months) was associated with worse outcomes including more severe and destructive arthritis (15).

Our study is one of the few conducted in the biological era that analyses predictors of time to relapse in a real-life clinical setting. In this regard, our findings suggested that the persistence of a

Table III. Univariate and multivariate COX regression analyses for demographical, clinical and biomarker variables for the outcomes earlier time to remission on medication, earlier time to remission off medication and earlier time to relapse.

Variable		Univariate COX regression		Multivariate COX regression	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Time to remission on medication					
Time from first symptom to diagnosis (days)	Continuous variable	0.992 (0.985-0.999)	0.035*	0.991 (0.984-0.999)	0.021*
Rash at Month 3	Yes	0.468 (0.255-0.860)	0.014*	0.962 (0.413-2.242)	0.929
	No	Ref	Ref	Ref	Ref
Elevated ferritin (>150ng/ml) at Month 3	Yes	0.528 (0.249-1.116)	0.094		
	No	Ref	Ref		
CID at Month 3	Yes	2.259 (1.323-3.857)	0.003*	2.102 (0.991-4.458)	0.053
	No	Ref	Ref	Ref	Ref
Elevated ferritin (>150ng/ml) at Month 6	Yes	0.261 (0.060-1.140)	0.074		
	No	Ref	Ref		
Steroids at diagnosis	Yes	0.594 (0.345-1.024)	0.061		
	No	Ref	Ref		
Anti-IL1 failure	Yes	0.368 (0.188-0.720)	0.004*	0.236 (0.158-0.672)	0.002*
	No	Ref	Ref	Ref	Ref
Time to remission off medication					
Rash at Month 3	Yes	0.312 (0.120-0.813)	0.017*	1.079 (0.255-4.572)	0.917
	No	Ref	Ref	Ref	Ref
CID At Month 3	Yes	4.405 (1.975-9.823)	<0.001*	3.506 (1.045-11.760)	0.042*
	No	Ref	Ref	Ref	Ref
Anakinra at diagnosis	Yes	0.482 (0.229-1.011)	0.054		
	No	Ref	Ref		
Anti-IL1 failure	Yes	0.113 (0.027-0.480)	0.003*	0.153 (0.035-0.661)	0.012*
	No	Ref	Ref	Ref	Ref
Relapses, number	Continuous variable	0.516 (0.254-1.050)	0.068		
Time to relapse					
Gender	Male	0.229 (0.063-0.834)	0.025*	0.247 (0.66-0.933)	0.039*
	Female	Ref	Ref	Ref	Ref
Rash at month 3	Yes	5.847 (1.899-18.000)	0.002*	5.763 (1.796-18.498)	0.003*
	No	Ref	Ref	Ref	Ref
Anti-IL1 failure	Yes	3.081 (1.035-9.176)	0.043*	1.981 (0.640-6.133)	0.236
	No	Ref	Ref	Ref	Ref

HR: hazard ratio, CI: confidence interval, CID: clinical inactive disease, WBC: white blood cells, IL: interleukin.

rash after 3 months was significantly associated with a shorter time to relapse, while the male gender was associated with a longer time to relapse. According to our analysis, a diagnostic delay leading to subsequent therapeutic delay and anti-IL1 treatment failure played a significant predictive role in a longer time to achieve remission while on medication. Few studies investigated the predictors of sJIA clinical course. A previous study, conducted in the pre-biologic era (1/45 patients treated with anakinra) and published in 2006 (2) reported that polyarticular arthritis at onset and the evidence of ongoing disease activity at 3 and 6 months were associated with a longer time to remission and a persistent disease course. Our study is the first investigating sJIA predictors of time to remission conducted in the biological era. Since diagnostic delay has been reported to negatively affect the time to achieve remission, this data underscores the importance of starting therapy promptly in order to adequately manage the disease course and treatment response. Treatment delay, especially delay in initiating IL-1 inhibitors, showed a trend toward worse outcomes, though delays in NSAID or glucocorticoid initiation were not significant predictors.

In our cohort, anti-IL1 non-responders exhibited a higher frequency of polyarthritis, a non-monophasic course, a higher number of relapses, and a longer time to achieve remission on treatment. Additionally, a longer time interval before starting anti-IL1 therapy among non-responders was reported, although not statistically significant. This finding appears to be in favour of the specula-

Table IV. Demographic and clinical features of patients treated with IL-1 inhibition.

	Patients treated with anti-IL1 (n=42)	Responders (n=27)	Non-responders (n=15)	*p*-value
Gender, male	19 (45.2%)	14 (51.8%)	5 (33.3%)	0.248
Age at diagnosis, years	6 (3-9.75)	7 (3.5-11.5)	3 (1.5-7.5)	0.040*
Interval to anti-IL1 start (days)	33.5 (18-82)	27 (15-67)	56 (20-118)	0.098
Complications	13 (30.9%)	6 (22.2%)	7 (46.7%)	0.101
Non-monophasic course	23 (54.8%)	9 (33.3%)	14 (93.3%)	< 0.001*
Number of relapses	0 (0-1)	0 (0-0)	1.5 (0.75-3)	0.010*
Remission on medication	38 (90.5%)	26 (96.3%)	12 (80%)	0.085
Time to remission on medication, months	2 (1-3)	1.75 (1-2)	4.5 (3-7)	< 0.001*
Remission off medication	17 (40.5%)	15 (55.5%)	2 (13.3%)	0.008*
Diagnosis				
Polyarthritis	9 (21.4%)	3 (11.1%)	6 (40%)	0.029*
Knee arthritis	10 (23.8%)	3 (11.1%)	7 (46.7%)	0.010*
Pericarditis	6 (14.3%)	2 (7.4%)	4 (26.7%)	0.087
Lymphoadenopathy	9 (21.4%)	8 (29.6%)	1 (6.7%)	0.082
Pharyngodynia	8 (19%)	8 (29.6%)	0 (0%)	0.019*
Lymphocyte count	2205 (1635-3000)	1900 (1307-2700)	2890 (2150-4105)	0.007*
NLR	7.76 (2.51-7.67)	5.68 (3.81-9.08)	4.1 (2.06-4.79)	0.037*
Eleveted AST	9 (21.4%)	4 (14.8%)	5 (33.3%)	0.053
Ferritin (ng/ml)	1150 (402-4464)	1036 (402-2863)	2175 (334-5269)	0.708
Steroids	34 (80.9%)	20 (74.1%)	14 (93.3%)	0.128
Month 3				
Arthritis	6 (14.3%)	1 (3.7%)	5 (33.3%)	0.009*
Number of active joints	0 (0-0)	0 (0-0)	0 (0-4.5)	0.018*
Elevated CRP (>1mg/dl)	12 (28.6%)	5 (18.5%)	7 (46.7%)	0.053
CRP (mg/dl)	0.23 (0.075-1.845)	0.2 (0.06-0.525)	1.16 (0.23-5.2)	0.027*
Elevated ferritin (>150ng/ml)	10 (23.8%)	4 (14.8%)	6 (53.3%)	0.018*
Ferritin (ng/ml)	60 (24.25-157.25)	38 (24-74)	305 (62-865)	0.037*
Oral steroids	25 (59.5%)	13 (48.1%)	12 (80%)	0.044*
CID	21 (50%)	17 (63%)	4 (26.7%)	0.024*
Clinical active disease	16 (38.1%)	7 (25.9%)	9 (60%)	0.029*
Month 6				
Arthritis	3 (7.1%)	0 (0%)	3 (40%)	0.016*
Number of active joints	0 (0-0)	0 (0-0)	0 (0-0)	0.017*
Elevated ferritin (>150ng/ml)	2 (4.8%)	0 (0%)	2 (13.3%)	0.011*
Oral GC	17 (40.5%)	5 (18.5%)	12 (80%)	< 0.001*

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, CID: clinical inactive disease, IL: interleukin, GC: glucocorticoid, NLR: neutrophil-to-lymphocyte ratio.

tion that IL-1 plays a crucial role, acting as the main inflammatory mediator during the initial phases of sJIA. Therefore, according to the 'window of opportunity' hypothesis, the early anti-IL1 treatment could potentially modify the natural history of the sJIA pathophysiology: inducing a rapid remission of systemic symptoms may prevent the progression to chronic arthritis, and the need for long-term treatment. Consequently, the reduced efficacy of a late introduction of IL-1 treatment may be explained by the emergence of the T cell-mediated response that sustains articular and systemic inflammation (3). In this perspective, the timing of anti-IL1 therapy initiation seems to significantly affect and contribute to the achievement of an effective response.

In this regard, Pardeo *et al*. reported that the only variable significantly associated with response to anakinra treatment in 25 sJIA patients was the time from disease onset to anti-IL1 administration, with earlier treatment being associated with a better outcome (14/25 patients who achieved CID) (16). In addition, Saccomanno *et al*. (17) demonstrated that sJIA response to anakinra was associated with shorter disease duration and less severe polyarthritis.

This evidence aligns with the Dutch experience, which provides long-term outcome data on the early use of anakinra in sJIA (18-20). The use of first-line monotherapy with anakinra led to early and sustained inactive disease in the majority of sJIA patients. Furthermore, a high neutrophil count at baseline and a complete response after one month of rIL-1Ra treatment were reported to be strongly associated with inactive disease at one year.

While our findings support the 'window of opportunity' theory, we also acknowledge the heterogeneity of sJIA. The association between polyarthritis and IL-1 failure may indicate a distinct biological phenotype less responsive to IL-1 blockade. Early age at onset, which was more frequent among non-responders, aligns with data suggesting an increased risk for severe or refractory forms, including sJIA-LD.

Several caveats hamper the conclusion of the analysis of our cohort: the retrospective data collection bias and the heterogeneous follow-up duration. The classification into monophasic and non-monophasic forms is limited by follow-up duration and treatment effects. It is possible that early therapeutic interventions may mask the natural course of disease, and our median follow-up of 22 months is insufficient to draw definitive

conclusions about long-term trajectories. Finally, considering the possibility of a monophasic disease course, it cannot be ruled out that some patients might have achieved remission regardless of the treatment.

Including 'IL-1 failure' as a variable in predicting a longer time to remission may not contribute to optimising early treatment decisions. However, it could enhance patient management by identifying individuals at higher risk of requiring prolonged therapy and more intensive follow-up to prevent complications. In this regard, a major limitation of the study is the short follow-up period, which limits the ability to assess long-term outcomes. Conversely, the ability to predict non-response to IL-1 therapy could be more impactful for early treatment optimisation, allowing for earlier consideration of alternative therapeutic strategies.

Another limitation of our study is the lack of serial assessment of serum biomarkers (*e.g.* IL-18, S100A, CXCL9, CXCL10), which would have allowed us to evaluate their role as predictors. However, our sJIA patients belong to a historical cohort spanning the last 6 years, and therefore, these data were not available. Additionally, we aimed to depict the long-term clinical course of a representative sJIA cohort in daily clinical practice, addressing the role of a timely starting treatment focusing on a real-life setting. A prospective study testing these biomarkers is currently ongoing at our centres.

However, through a comprehensive patients data analysis, we aimed to add new clinical insights into potential factors influencing the sJIA course in a real-life setting. The identification of clinical risk factors may represent a useful tool contributing to the development of tailored treatment plans for routine clinical care of sJIA patients. Further studies involving larger cohorts and coupling prospective results of current available biomarkers are required to validate our findings. The present clinical data derived from a real-life clinical setting might contribute to adding information for a more comprehensive understanding of sJIA pathophysiology and its clinical course.

Conclusions

Our findings highlight that diagnostic and therapeutic delay, as well as IL-1 treatment failure, negatively affect outcomes in sJIA. These factors may contribute to a more refined patient stratification, enabling the early identification of individuals who may benefit from more aggressive treatment and closer clinical and laboratory monitoring. However, further prospective studies are needed to better define precise disease trajectories and to correlate clinical features with laboratory findings. This is essential to validate the role of biomarkers in predicting treatment response and the risk of flare upon therapy discontinuation.

Acknowledgments

This study was supported in part by funds from the 'Current Research Annual Funding' of the Italian Ministry of Health

References

1. TARP S, AMARILYO G, FOELDVARI I *et al*.: Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. *Rheumatology* (Oxford) 2016; 55(4): 669-79. https://doi.org/10.1093/rheumatology/kev382
2. 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; 54(5): 1595-601. https://doi.org/10.1002/art.21774
3. NIGROVIC PA: Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? *Arthritis Rheumatol* 2014; 66(6): 1405-13. https://doi.org/10.1002/art.38615
4. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31(2): 390-92.
5. MARTINI A, RAVELLI A, AVCIN T *et al*.: Toward new classification criteria for juvenile idiopathic arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. *J Rheumatol* 2019; 46(2): 190-97. https://doi.org/10.3899/jrheum.180168
6. KIMURA Y, GREVICH S, BEUKELMAN T *et al*.: Pilot study comparing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) systemic Juvenile Idiopathic Arthritis Consensus Treatment Plans. *Pediatr Rheumatol Online J* 2017; 15: 23. https://doi.org/10.1186/s12969-017-0157-1
7. DEWITT EM, KIMURA Y, BEUKELMAN T *et al*.: Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res* 2012; 64(7): 1001-10. https://doi.org/10.1002/acr.21625
8. KOKER O, DEMIRKAN FG, CAKMAK F, AKTAY AYAZ N: Performance of recent PRINTO criteria versus current ILAR criteria for systemic juvenile idiopathic arthritis: a single-centre experience. *Mod Rheumatol* 2023; 33(1): 187-93. https://doi.org/10.1093/mr/roab115
9. CALABRO JJ, HOLGERSON WB, SONPAL GM, KHOURY MI: Juvenile rheumatoid arthritis: a general review and report of 100 patients observed for 15 years. *Semin Arthritis Rheum* 1976; 5(3): 257-98. https://doi.org/10.1016/0049-0172(76)90027-5
10. FANTINI F, GERLONI V, GATTINARA M, CIMAZ R, ARNOLDI C, LUPI E: Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. *J Rheumatol* 2003; 30(3): 579-84.
11. 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; 27(2): 491-96.
12. WALLACE CA, LEVINSON JE: Juvenile rheumatoid arthritis: outcome and treatment for the 1990s. *Rheum Dis Clin North Am 1*991; 17(4): 891-905.
13. BARIS HE, ANDERSON E, SOZERI B, DEDEOGLU F: Impact of biologics on disease course in systemic onset juvenile idiopathic arthritis. *Clin Rheumatol* 2018; 37(12): 3263-73. https://doi.org/10.1007/s10067-018-4297-6
14. BEHRENS EM, BEUKELMAN T, GALLO L *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; 35(2): 343-48.
15. RUSSO RAG, KATSICAS MM: Patients with very early-onset systemic juvenile idiopathic arthritis exhibit more inflammatory features and a worse outcome. *J Rheumatol* 2013; 40(3): 329-34. https://doi.org/10.3899/jrheum.120386
16. PARDEO M, MARAFON DP, INSALACO A *et al*.: Anakinra in systemic juvenile idiopathic arthritis: a single-center experience. *J Rheumatol* 2015; 42(8): 1523-27. https://doi.org/10.3899/jrheum.141567
17. SACCOMANNO B, TIBALDI J, MINOIA F *et al*.: Predictors of effectiveness of anakinra in systemic juvenile idiopathic arthritis. *J Rheumatol* 2019; 46(4): 416-21. https://doi.org/10.3899/jrheum.180331
18. VASTERT SJ, DE JAGER W, NOORDMAN BJ *et al*.: Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. *Arthritis Rheumatol* 2014; 66(4): 1034-43. https://doi.org/10.1002/art.38296
19. TER HAAR NM, VAN DIJKHUIZEN EHP, SWART JF *et al*.: Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. *Arthritis Rheumatol* 2019; 71(7): 1163-73. https://doi.org/10.1002/art.40865
20. HINZE CH, FOELL D, KESSEL C: Treatment of systemic juvenile idiopathic arthritis. *Nat Rev Rheumatol* 2023; 19(12): 778-89. https://doi.org/10.1038/s41584-023-01042-z