

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

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Objective. Systemic juvenile idiopathic arthritis (JIA) is a multifactorial autoinflammatory disease with a historically poor prognosis. With current treatment regimens, approximately half of patients still experience active disease after 1 year of therapy. This study was undertaken to evaluate a treat-to-target approach using recombinant interleukin-1 receptor antagonist (rIL-1Ra; anakinra) as first-line monotherapy to achieve early inactive disease and prevent damage.

Methods. In this single-center, prospective study, patients with new-onset systemic JIA with an unsatisfactory response to nonsteroidal antiinflammatory drugs received rIL-1Ra monotherapy according to a treat-to-target strategy. Patients with an incomplete response to 2 mg/kg rIL-1Ra subsequently received 4 mg/kg rIL-1Ra or additional prednisolone, or switched to alternative therapy. For patients in whom inactive disease was achieved, rIL-1Ra was tapered after 3 months and subsequently stopped.

Results. Forty-two patients, including 12 who had no arthritis at disease onset, were followed up for a median of 5.8 years. The median time to achieve inactive disease was 33 days. At 1 year, 76% had inactive disease, and 52% had inactive disease while not receiving medication. High neutrophil counts at baseline and a complete response after 1 month of rIL-1Ra were highly associated with inactive disease at 1 year. After 5 years of follow-up, 96% of the patients included had inactive disease, and 75% had inactive disease while not receiving medication. Articular or extraarticular damage was reported in <5%, and only 33% of the patients received glucocorticoids. Treatment with rIL-1Ra was equally effective in systemic JIA patients without arthritis at disease onset.

Conclusion. Treatment to target, starting with first-line, short-course monotherapy with rIL-1Ra, is a highly efficacious strategy to induce and sustain inactive disease and to prevent disease- and glucocorticoid-related damage in systemic JIA.

INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) is a multifactorial autoinflammatory disease, characterized by arthritis, quotidian spiking fevers, skin rash, lymphadenopathy, hepatomegaly,

splenomegaly, and/or serositis, in combination with a substantial increase in the inflammatory parameters erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and ferritin level (1). Systemic JIA is still classified under the umbrella of JIA (2), although it has been demonstrated that the mechanisms

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underlying the systemic inflammation in systemic JIA differ in important aspects from the other JIA subtypes (1). Analogous to adult-onset Still's disease, the requirement of arthritis for the diagnosis of systemic JIA is a subject of debate, since a substantial proportion of patients with systemic JIA do not present with arthritis at disease onset (3–6).

The natural course of systemic JIA is severe. Data from cohorts in the pre-biologics era showed that half of the patients had persistent active disease for years and articular damage was common; some investigators even reported joint replacements in 75% of systemic JIA patients (7–12). Disease-modifying antirheumatic drugs (DMARDs) that were beneficial in other subtypes of JIA were ineffective in systemic JIA, and patients with refractory disease relied on long-term glucocorticoid use, or autologous stem cell transplantation as a last resort (13–15).

The discovery of the involvement of the interleukin-1 (IL-1) and IL-6 pathways in systemic JIA led to the effective use of IL-1 and IL-6 signaling inhibition in these patients (16–20). Unfortunately, the first trials demonstrated completely inactive disease in only 30% of patients after the first year of therapy, and biologic therapy was often combined with other glucocorticoids and/or other DMARDs. In recent inception cohorts, ~50% of the patients with new-onset disease had inactive disease after 1 year and 70% after 3 years of therapy (21,22). In addition, 50–60% of patients with systemic JIA received long-term systemic glucocorticoids, which are associated with severe and longstanding side effects such as growth failure and obesity (21–23). Hence, there is a strong need for a more effective therapeutic approach with fewer side effects.

Several studies of systemic JIA have indicated that, especially in the early phase of this disease, activation of the innate immune system, including activation of the IL-1 pathway, is most prominent (16,24,25). IL-1 blocking therapy specifically would be favorable during this so-called “window of opportunity” (24). In 2008 we initiated a prospective trial of recombinant IL-1 receptor antagonist (rIL-1Ra) as first-line monotherapy for patients with new-onset systemic JIA, in which inactive disease was achieved in 85% of the patients within 1 year (26). Furthermore, we described a strategy to taper and stop rIL-1Ra treatment in patients with inactive disease (26). In the present study, we investigated the long-term efficacy of our treat-to-target approach using rIL-1Ra as first-line monotherapy.

PATIENTS AND METHODS

Patients. We included patients who presented to University Medical Center Utrecht (UMCU) with a new diagnosis of systemic JIA from 2008 until 2017. In addition to the patients included in our previous study (26), the present study also included patients who presented since January 2012 and patients who were seen with arthralgia but without overt arthritis at diagnosis from the start of the cohort in 2008. The latter were only included if the clinical picture (e.g., spiking fever, rash) and laboratory values (e.g., ferritin

and IL-18 levels) indicated a suspected diagnosis of systemic JIA and when other diagnoses such as infections and malignancies had been excluded by extensive diagnostic procedures, including microbial investigations (cultures, serology, and polymerase chain reaction), imaging (abdominal ultrasound, positron emission tomography–computed tomography scanning, etc.), and genetic tests (for periodic fever syndromes). Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>) provides more detailed information on the symptoms and diagnostic evaluation of the patients without arthritis at onset.

Study design. The therapeutic treat-to-target strategy with rIL-1Ra as first-line monotherapy has been described previously (26). Briefly, when patients had an unsatisfactory response (persistence of fever and arthritis after 7 days of treatment) to indomethacin (or an equivalent nonsteroidal antiinflammatory drug [NSAID]), rIL-1Ra was initiated at a dosage of 2 mg/kg/day (with a maximum of 100 mg/day in patients weighing ≥ 50 kg) subcutaneously. If fever persisted after 3 days, the rIL-1Ra dosage was increased to 4 mg/kg/day (maximum of 200 mg/day). In patients who had persistent disease activity while receiving rIL-1Ra monotherapy, prednisolone 0.5–1 mg/kg/day was added and/or patients were switched to alternative biologic agents, such as canakinumab 4 mg/kg or tocilizumab 8 mg/kg (for patients >30 kg) or 12 mg/kg (for patients <30 kg).

If patients had inactive disease at 3 months while receiving rIL-1Ra only, rIL-1Ra was tapered for a month (alternate-day regimen) and subsequently stopped. When a disease flare occurred, rIL-1Ra was restarted. When multiple attempts at tapering failed, canakinumab was offered in order to avoid daily injections. Patients were monitored for adverse events or side effects such as infection and local skin reactions. Institutional review board approval was obtained by the UMCU ethics committee (study no. 08-215), and informed consent was given by patients and/or their parents.

Analysis of blood and serum samples. Blood was drawn for routine laboratory measurements at disease onset, before the initiation of rIL-1Ra treatment, and at all follow-up visits. Data regarding complete blood cell counts were extracted from the Utrecht Patient-Oriented Database (27). Serum concentrations of IL-18 at disease onset were determined using a validated (ISO 9001 certified) multiplex immunoassay, as previously described (28).

Outcome measures. The primary outcome measure for this study was clinically inactive disease 1 year after the initiation of rIL-1Ra. Clinically inactive disease was defined according to the modified Wallace criteria as the absence of arthritis, morning stiffness, and systemic features; a physician's global assessment indicating no disease activity (<10 on a scale of 0–100); and normalization of ESR (<20 mm/hour) and CRP level (<10 mg/liter) (29). Secondary outcome measures 1 year after the initiation of

rIL-1Ra were the percentage of patients in whom inactive disease was achieved with rIL-1Ra monotherapy and the percentage of patients with inactive disease while not receiving medication. In addition, the percentage of patients with inactive disease was assessed at 1 month, 3 months, 3 years, and 5 years after the initiation of therapy, and the date of the first visit with inactive disease was recorded to determine the time to achieve inactive disease. At the last follow-up visit, disease activity, medication use, growth, damage, and patient-reported outcome measures were assessed. Growth measurements included height, weight, and body mass index (BMI) and were expressed as standard deviations from the mean in the healthy Dutch population. A short stature was defined as height less than -2 SD for age, obesity was defined as BMI >2 SD for age, and underweight was defined as BMI less than -2 SD for age. Disease- and therapy-associated damage was assessed annually using the Juvenile Arthritis Damage Index (30). Patient-reported outcomes were investigated using the Juvenile Arthritis Multidimensional Assessment Report and included patient-reported pain, disease severity, well-being, quality of life, and functional ability (31,32).

Statistical analysis. Continuous variables are presented as the median (interquartile range [IQR]). Differences between 2 groups were analyzed by Mann-Whitney U test, and correlations were determined by Spearman's rho. Differences in categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test, as appropriate. Time to inactive disease or flare was assessed using the Kaplan-Meier method. To determine factors associated with the achievement of inactive disease at 1 year, clinical and biochemical markers with a P value less than 0.05 for the comparison between patients with active disease and those with inactive disease at 1 year in univariate analysis were entered into a multivariable binomial logistic regression model. If variables correlated strongly (Spearman's rho >0.6), the variable with the lowest P value was chosen. Furthermore, principal components regression was used to achieve dimension reduction. Goodness-of-fit of the models was assessed by the area under the curve (AUC) of the receiver operating characteristic curve. For significant continuous variables, an optimal cutoff was determined by choosing the highest sum of specificity and sensitivity. Internal validation of the models was performed by leave-one-out cross-validation. Basic statistical analyses were performed using IBM SPSS Statistics version 21. For principal components analysis and modeling, R, version 3.4.1 was used, including the packages "devtools," "ggplot2," "factoextra," and "pROC."

RESULTS

Baseline characteristics of the patients. Between 2008 and 2017, 51 patients with new-onset systemic JIA presented to UMCU. Once the diagnosis was established and

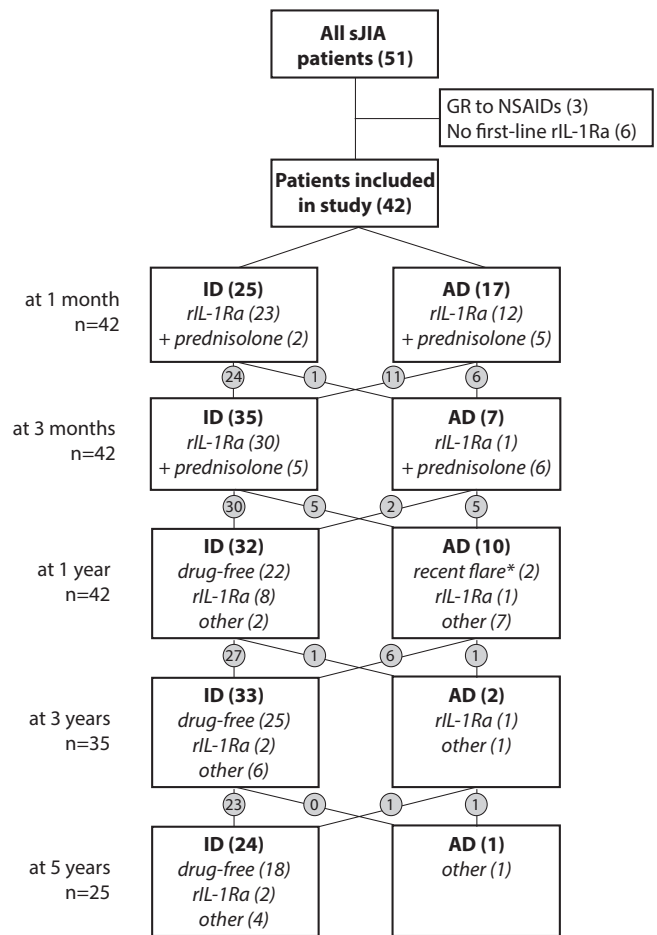


Figure 1. Flow chart showing the disposition of the patients with systemic juvenile idiopathic arthritis (sJIA) and their response to first-line recombinant interleukin-1 receptor antagonist (rIL-1Ra) therapy. Values in circles are the number of patients. * = The 2 patients with recent flares experienced recurrent disease activity after ~1 year; no therapy had been initiated. GR = good response; NSAIDs = nonsteroidal antiinflammatory drugs; ID = inactive disease; AD = active disease.

when NSAIDs were not effective, monotherapy with rIL-1Ra was initiated. After the exclusion of patients who had received previous DMARDs or glucocorticoids ($n = 6$) and patients with a good response to NSAIDs ($n = 3$), 42 patients entered the study (Figure 1). The median age at onset of systemic JIA was 7 years, and 60% of the patients were male (Table 1). Patients were treated with rIL-1Ra a median of 30 days after the first manifestation of symptoms.

Similar clinical and immunologic characteristics of patients with systemic JIA with arthritis and those without arthritis at onset. As mentioned above, the requirement of chronic arthritis for the diagnosis of systemic JIA is a matter of debate (3,4). In our cohort, 12 patients (29%) had a clinical phenotype compatible with the diagnosis of systemic JIA but without arthritis at onset. During follow-up,

Table 1. Baseline characteristics of the patients with systemic JIA with arthritis and those without arthritis at onset*

Clinical information	All JIA patients (n = 42)	JIA patients with arthritis (n = 30)	JIA patients without arthritis (n = 12)
Age at start of rIL-1Ra treatment, years	7.1 (3.9, 11.8)	7.9 (4.1, 12.2)	5.2 (3.7, 10.9)
Sex, no. male/female	25/17	17/13	8/4
Duration between first symptom and start of rIL-1Ra treatment, days	30 (19, 61)	31 (21, 65)	25 (16, 49)
Fever, %	100	100	100
Rash, %	88.1	93.3	75
Lymphadenopathy, %	57.1	50	75
Hepatomegaly, %	38.1	33.3	50
Splenomegaly, %	19.0	16.7	25
Serositis, %	9.5	10	8.3
No. of joints with active disease	2 (0, 4)	3 (2, 4)	0 (0, 0)†
Physician's global assessment	40 (30, 49)	40 (30, 50)	40 (28, 40)
ESR, mm/hour	106 (83, 131)	107 (87, 135)	101 (81, 109)
CRP, mg/liter	138 (93, 225)	156 (103, 233)	116 (78, 207)
Ferritin, µg/liter	656 (284, 2,354)	672 (284, 2,354)	648 (250, 3,385)
Hemoglobin, mmol/liter	6.1 (5.7, 6.5)	6.1 (5.4, 6.6)	6.2 (5.8, 6.5)
Leukocytes, × 10 ⁹ /liter	18.8 (12.5, 26.2)	18.0 (12.3, 25.4)	20.90 (12.85, 30.18)
Neutrophils, × 10 ⁹ /liter	14.61 (8.51, 22.07)	13.60 (8.20, 21.34)	18.32 (9.89, 26.03)
Lymphocytes, × 10 ⁹ /liter	2.54 (1.83, 23.20)	2.60 (2.07, 3.33)	2.13 (1.52, 2.81)
Monocytes, × 10 ⁹ /liter	0.67 (0.52, 0.83)	0.66 (0.47, 0.81)	0.79 (0.52, 0.93)
Platelets, × 10 ⁹ /liter	603 (375, 707)	576 (376, 688)	623 (286, 805)

* Except where indicated otherwise, values are the median (interquartile range). Ordinal variables were compared using Fisher's exact test and continuous variables were compared using the Mann-Whitney U test. rIL-1Ra = recombinant interleukin-1 receptor antagonist; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

† $P < 0.001$ versus patients with juvenile idiopathic arthritis (JIA) with arthritis. All other comparisons were nonsignificant.

4 patients developed arthritis during disease flares, 2 patients experienced a febrile flare without arthritis, and 6 patients never had a flare. No differences in clinical characteristics or laboratory values were observed between patients with and those without arthritis at onset (Table 1). After extensive diagnostic procedures to exclude other diseases, these patients were treated and followed up in the same manner as patients with "regular" systemic JIA. (See Supplementary Table 1, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>, for details of the diagnostic evaluation.) Of note, all patients without arthritis at onset ultimately fulfilled the proposed new Paediatric Rheumatology International Trials Organisation (PRINTO) classification criteria for systemic JIA (33). To enable comparison with other studies, we show most outcome data for patients with and those without arthritis in separate tables.

Early induction of inactive disease by rIL-1Ra as first-line monotherapy. Monotherapy with rIL-1Ra as a first-line agent was highly effective in patients with new-onset systemic JIA. After only 1 month of therapy, 23 patients (55%) had completely inactive disease while receiving rIL-1Ra monotherapy, and 2 patients had inactive disease while receiving rIL-1Ra combined with prednisolone (Figure 1). After 3 months

of therapy, 35 patients (83%) had inactive disease, 30 of whom (20 of 30 patients with arthritis and 10 of 12 patients without arthritis) reached inactive disease with rIL-1Ra monotherapy, without the use of glucocorticoids (Figure 1 and Table 2). Of these 30 patients, inactive disease was achieved in 29 with rIL-1Ra 2 mg/kg and in 1 with rIL-1Ra 4 mg/kg. Figure 2A clearly depicts that the patients who responded to monotherapy with rIL-1Ra all reached inactive disease within 100 days (median time 28 days), while the majority of those who needed additional prednisolone reached inactive disease after those 100 days, if at all, within 1 year (median time 122 days) ($P < 0.001$ by log rank test). The median time to achieve inactive disease in the whole cohort was 33 days; 95% of the patients experienced a period of inactive disease in the first year.

Sustained inactive disease after a short course of rIL-1Ra. After a median period of 3.7 months, rIL-1Ra tapering was started in 33 patients. Two of these patients experienced recurrent disease activity while rIL-1Ra was being tapered and continued IL-1 blockade. Thirty-one patients were able to stop rIL-1Ra, and 29 of them did so within the first year of therapy. The median total duration of rIL-1Ra treatment was 6.1 months (IQR 4.4, 9.5 months). Eighteen of the 31 patients remained free

Table 2. Disease activity and treatments for patients with systemic JIA with arthritis and those without arthritis at onset*

Time point and treatment	JIA patients with arthritis at onset (n = 30)		JIA patients without arthritis at onset (n = 12)	
	Inactive disease	Active disease	Inactive disease	Active disease
1 month	15 (50.0)	15 (50.0)	10 (83.3)	2 (16.7)
rIL-1Ra	14	11	9	1
rIL-1Ra + GC	1	4	1	1
3 months	24 (80.0)	6 (20.0)	11 (91.7)	1 (8.3)
rIL-1Ra	20	1	10	0
rIL-1Ra + GC	3	4	1	1
rIL-1Ra + MTX + GC	1	0	0	0
MTX + GC	0	1	0	0
1 year	20 (67.7)	10 (33.3)	12 (100)	0 (0)
No therapy	0	2†	0	0
Drug-free	14	0	8	0
rIL-1Ra	5	1	3	0
MTX + GC	1	0	0	0
Canakinumab	0	3	0	0
Tocilizumab	0	3	1	0
Etanercept	0	1	0	0
3 years‡	23 (95.8)	1 (4.2)	10 (90.9)	1 (9.1)
Drug-free	17	0	8	0
rIL-1Ra	2	0	0	1
Canakinumab	1	1	1	0
Tocilizumab	2	0	1	0
MTX	1	0	0	0
5 years§	21 (100)	0	3 (75)	1 (25)
Drug-free	15	0	3	0
rIL-1Ra	2	0	0	0
Canakinumab	2	0	0	0
Tocilizumab	1	0	0	1
Intraarticular GCs, NSAID	1	0	0	0

* Values are the number (%) of patients. Canakinumab and tocilizumab were often combined with low-dose prednisolone. JIA = juvenile idiopathic arthritis; rIL-1Ra = recombinant interleukin-1 receptor antagonist; GC = glucocorticoid; MTX = methotrexate; NSAID = nonsteroidal antiinflammatory drug.

† Patients had experienced recent flares, and no therapy had been initiated yet.

‡ Six of 30 patients with arthritis and 1 of 12 patients without arthritis had <3 years of follow-up; of these, 1 patient with arthritis at onset died due to macrophage activation syndrome.

§ Nine of 30 patients with arthritis and 8 of 12 patients without arthritis had <5 years of follow-up.

of flares after stopping rIL-1Ra (including 2 patients who received rIL-1Ra for >1 year) and have been in remission without therapy for years (Figure 2B). Thirteen of the 31 patients experienced a flare after stopping rIL-1Ra. The median time to flare was 5 weeks (IQR 3 weeks, 5 months) Three patients had a flare in the first week after stopping rIL-1Ra, and 3 patients experienced a late flare (9 months to 5 years after stopping rIL-1Ra). Flares often subsided after reinstitution of rIL-1Ra; 3 patients were able to stop rIL-1Ra again within the first year of therapy, 4 others had inactive disease while receiving rIL-1Ra at 1 year, and 2 patients experienced a flare around the 1-year time point. In addition, 1 patient

stopped rIL-1Ra but continued to receive methotrexate (MTX) and prednisolone.

In total, 32 patients (76%) had inactive disease 1 year after the initiation of rIL-1Ra; 22 of these patients (52% of the whole cohort) were not receiving therapy. Of these 32 patients, 28 had only received rIL-1Ra, 2 had received rIL-1Ra and prednisolone, 1 had received MTX and prednisolone (in addition to previously receiving rIL-1Ra), and 1 patient switched to tocilizumab and prednisolone (Figure 1 and Table 2). Patients without arthritis at onset had better outcomes at 1 year: 20 (67%) of 30 patients with arthritis and all 12 patients without arthritis at onset had inactive

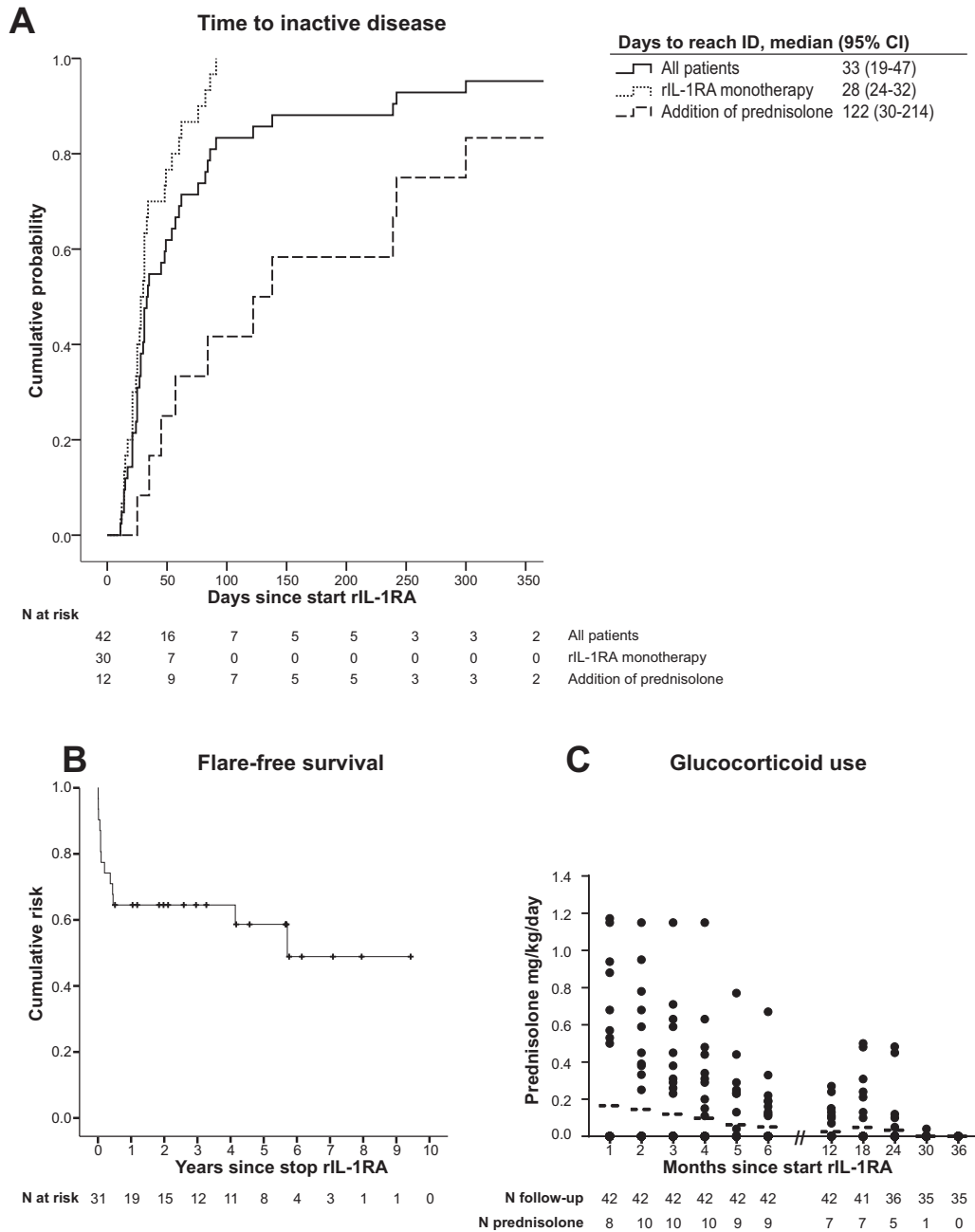


Figure 2. Response of patients with systemic juvenile idiopathic arthritis (JIA) to recombinant interleukin-1 receptor antagonist (rIL-1Ra). **A**, Kaplan-Meier curve of the time to achieve inactive disease (ID). Curves are shown for all patients with systemic JIA (n = 42), patients receiving rIL-1Ra monotherapy (n = 30), and patients who needed prednisolone in addition to rIL-1Ra to achieve inactive disease (n = 12). 95% CI = 95% confidence interval. **B**, Kaplan-Meier curve of flare-free survival time, defined as the time until first flare, censored at the last follow-up if no flare occurred. Data are included for 31 patients who stopped receiving rIL-1Ra due to inactive disease. **C**, Glucocorticoid use in the first 3 years of IL-1Ra therapy. Circles represent individual patients, except for the circles shown for 0.0 mg/kg/day, which each represent 31–35 patients who were not receiving prednisolone at the indicated time point, as indicated by the numbers below the figure.

disease; 14 (47%) of the 30 patients with arthritis and 8 (67%) of the 12 patients without arthritis were not receiving therapy.

High rate of sustained remission during long-term follow-up. Long-term follow-up, with 35 patients followed up for 3 years and 25 patients followed up for 5 years, showed sustained high response rates. Of the patients followed up for 5

years, 96% (24 of 25) had inactive disease, and 18 of these 24 patients (75%) were not receiving medication, at 5 years (Figure 1 and Table 2). One patient with severe disease refractory to rIL-1Ra, MTX, tocilizumab, canakinumab, and glucocorticoids died due to macrophage activation syndrome with neurologic symptoms and pulmonary hypertension 2 years after the start of therapy. Other than in this patient, no pulmonary complica-

tions were observed. In total, 4 patients in our cohort (9.5%) developed macrophage activation syndrome during their disease course. Inactive disease was not achieved with rIL-1Ra in 3 of these 4 patients, and they were therefore switched to alternative therapies in the first year of treatment. One patient had a good response to rIL-1Ra and clinically inactive disease was achieved prior to the onset of macrophage activation syndrome. Both macrophage activation syndrome episodes in this patient seemed to be triggered by viral infections (in 1 episode we identified a primary infection with Epstein-Barr virus as the trigger). (For additional details on macrophage activation syndrome episodes, see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>.)

Limited use of glucocorticoids to achieve or sustain inactive disease. An important goal of our therapeutic strategy was to minimize glucocorticoid use. Indeed, only one-third of the patients ($n = 14$; 11 of 30 patients with arthritis and 3 of 12 without arthritis) received systemic glucocorticoids to achieve or sustain inactive disease (Figure 2C). Of these 14 patients, 7 received high-dose prednisolone (≥ 1 mg/kg/day), which was indicated for clinical deterioration despite rIL-1Ra treatment and/or as treatment for macrophage activation syndrome. In 5 patients with an incomplete response to rIL-1Ra monotherapy, prednisolone 0.5 mg/kg was added within the

first 2 months of therapy. Additionally, 2 patients received prednisolone 0.2–0.3 mg/kg as add-on therapy along with rIL-1Ra or canakinumab later in the disease course. In total, more than half of the patients ($n = 24$; 17 of 30 patients with arthritis and 7 of 12 without arthritis) needed only rIL-1Ra and NSAIDs to achieve and sustain inactive disease during follow-up. Fourteen patients (33%) switched to other biologic agents or MTX combined with steroids; reasons for switching were incomplete response to rIL-1Ra or a prolonged need for therapy. No patient stopped rIL-1Ra due to infections or other severe adverse events. Table 2 shows the response to therapy over time during follow up.

Minimal damage and good quality of life at time of last follow-up. At the time of the last follow-up, a median of 5.8 years (IQR 2.9, 7.6 years) after the initiation of rIL-1Ra, inactive disease had been achieved in 36 (86%) of 42 patients. Only 2 patients (5%) had articular damage (both of these patients had presented with arthritis at disease onset) (Table 3). None of the patients in our cohort developed growth failure during follow-up; 1 patient with Down syndrome and a preexisting short stature had a height that remained more than 2 SD below the mean in the healthy population. Five patients (12%) were obese (defined as a BMI of >25) at last follow-up, of whom 4 were obese at disease onset (prior to treatment). Two patients (5%) had extraarticular damage (short stature and striae); both of these patients had received glucocorticoids.

Table 3. Overview of outcome measures in the patients with systemic JIA at last follow-up*

	Median (IQR)	Score, % of patients		
		<-2SD/>2SD	Best score (0)	Top 10% score
Growth ($n = 42$)†				
Height	-0.4 (-1.2, 0.3)	2.4/-	-	-
Weight	0.3 (-0.5, 1.1)	4.8/9.5	-	-
BMI	0.6 (-0.2, 1.5)	2.4/11.9	-	-
Damage ($n = 41$)‡				
Articular (range 0–72)	0 (0, 0)	-	95	100
Extraarticular (range 0–17)	0 (0, 0)	-	95	100
Patient-reported outcome measures§				
Pain ($n = 39$) (range 0–100)	0 (0, 4)	-	62	79
Severity ($n = 39$) (range 0–100)	0 (0, 2)	-	62	79
Well-being ($n = 36$) (range 0–100)	0 (0, 4)	-	58	81
Functionality ($n = 36$) (range 0–30)	0 (0, 1)	-	69	94
Quality of life ($n = 34$) (range 0–30)	2 (0, 5)	-	35	65

* The median follow-up time was 5.8 years. Separate data for patients with and those without arthritis are shown in Supplementary Table 3 (online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>). JIA = juvenile idiopathic arthritis; IQR = interquartile range; BMI = body mass index.

† Scores for growth are based on the SD from the mean in the age-matched healthy population.

‡ Measured by Juvenile Arthritis Damage Index.

§ Pain, disease severity, and well-being scoring systems were derived from the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) or the Childhood Health Assessment Questionnaire, functionality was determined using the Juvenile Arthritis Functionality Score, and quality of life was determined using the Paediatric Rheumatology Quality of Life scale, derived from JAMAR.

Consistent with the highly efficacious therapeutic response, patient-reported outcome measures at last follow-up indicated a normal quality of life in the majority of patients (Table 3). Sixty-two percent of the patients reported a complete absence of pain and disease. The best possible score for well-being was given by 58% of patients, and the best possible score for functional ability by 69%. Furthermore, 35% rated their quality of life as the best possible and 65% rated it as good (a score in the top 10%). Scores for patient-reported outcome measures were similar in patients with and those without arthritis (Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>).

Baseline neutrophil counts as a predictor of inactive disease at 1 year. With the goal of developing a prediction model for rIL-1Ra response (defined as clinically inactive disease at 1 year), we performed a univariate analysis that demonstrated that patients in whom inactive disease was achieved at 1 year were younger and had a significantly shorter disease duration, fewer joints with active disease, and higher neutrophil and leukocyte counts prior to the start of rIL-1Ra treatment (Supplementary Table 4, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>). Disease duration and leukocyte and neutrophil count were also predictive of the response to IL-1Ra when

only patients with arthritis at disease onset were included in the analysis (Supplementary Table 5, <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>). Serum concentrations of IL-18 at disease onset did not predict disease activity status at 1 year.

For the secondary outcome measures (inactive disease while receiving rIL-1Ra monotherapy and inactive disease while not receiving medication at 1 year), neutrophil count and disease duration were significantly different (Supplementary Tables 4 and 5, <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>). As expected, we found a strong correlation between leukocyte count and neutrophil count (Spearman's $\rho = 0.979$), as well as between the active joint count and the presence or absence of arthritis (Spearman's $\rho = 0.797$); we selected neutrophil count and active joint count since they had the lowest *P* values. Further, a modest negative correlation was observed between disease duration and neutrophil count (Spearman's $\rho = -0.550$) (Figure 3A). Multivariate analysis using age, disease duration prior to the start of rIL-1Ra, active joint count, and neutrophil count prior to the start of rIL-1Ra as variables revealed that a high neutrophil count prior to the start of rIL-1Ra treatment was the best predictor of inactive disease at 1 year in our cohort (Supplementary Table 6, available on the available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>).

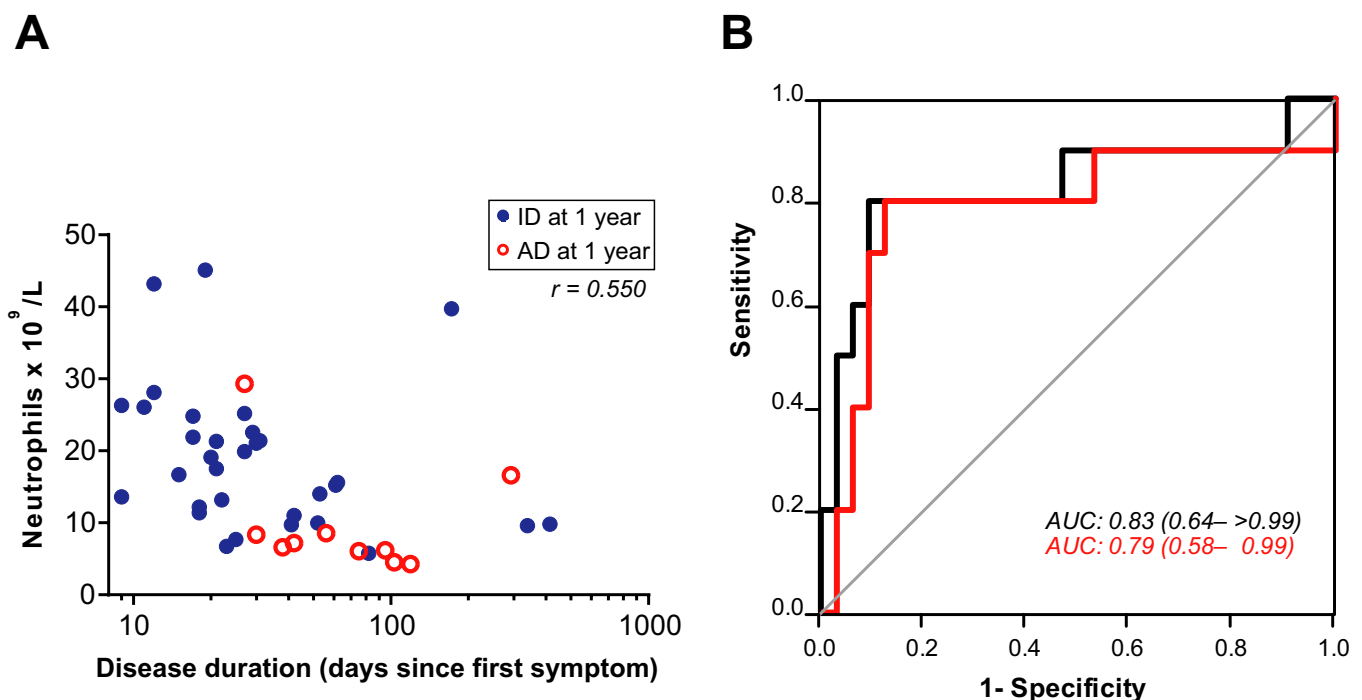


Figure 3. Relationship between neutrophil count, disease duration, and response to recombinant interleukin-1 receptor antagonist (rIL-1Ra) in patients with systemic juvenile idiopathic arthritis. **A**, Correlation between neutrophil count at the start of rIL-1Ra treatment and disease duration (time between first symptom and start of rIL-1Ra treatment) in patients with inactive disease (ID) at 1 year and patients with active disease (AD) at 1 year. Circles represent individual patients. **B**, Receiver operating characteristic curve of the whole data set (black line) and leave-one-out cross-validation (red line) with neutrophil count as the variable and inactive disease at 1 year as the outcome. AUC = area under the curve (with the 95% confidence interval shown in parentheses).

The model with only “neutrophil count” performed better than models using all 4 variables (Supplementary Table 6). Logistic regression for reaching inactive disease at 1 year based on neutrophil counts revealed an odds ratio (OR) of 1.19 (95% confidence interval [95% CI] 1.05, 1.42; $P = 0.021$), an AUC of 0.83 (95% CI 0.64, >0.99) in the whole data set, and an AUC of 0.79 (95% CI 0.58, 0.99) in the leave-one-out cross-validation (Figure 3B and Supplementary Table 6). The best cutoff (highest sum of sensitivity and specificity) was a neutrophil count of 9×10^9 /liter (sensitivity 0.91, specificity 0.80). Inactive disease was achieved after 1 year in 29 (94%) of 31 patients with a neutrophil count of $>9 \times 10^9$ /liter, compared to only 3 (27%) of 11 patients with a neutrophil count of $\leq 9 \times 10^9$ /liter (OR 38.67 [95% CI 6.53, 362.73]) ($P < 0.001$) (Supplementary Table 6, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40865/abstract>).

Early response associated with sustained inactive disease at 1 year. In addition to variables before the start of therapy, an early good response to rIL-1Ra was highly associated with sustained inactive disease at 1 year. Twenty-four (96%) of 25 patients in whom inactive disease was achieved at 1 month had sustained inactive disease at 1 year, compared to only 8 (47%) of 17 patients with active disease at 1 month (OR 27.0 [95% CI 4.17, 539.74], $P = 0.003$) (Supplementary Table 6). Patients with persistent arthritis after 1 month of rIL-1Ra treatment were especially at risk of prolonged disease activity; inactive disease was achieved in only 1 of these 6 patients at 1 year (OR 0.03 [95% CI 0.00, 0.25], $P = 0.004$) (Supplementary Table 6). Inactive disease was ultimately achieved in these 6 patients with tocilizumab ($n = 2$), canakinumab ($n = 2$), or the combination of MTX and prednisolone ($n = 2$). The ability to achieve inactive disease without glucocorticoids was also associated with sustained inactive disease at 1 year; 28 of 30 patients in whom inactive disease was achieved with rIL-1Ra monotherapy in the first 3 months had sustained inactive disease at 1 year, compared to only 4 of 12 patients who needed additional glucocorticoids to achieve inactive disease (OR 28.00 [95% CI 5.06, 240.21], $P < 0.001$) (Supplementary Table 6).

Taken together, our data demonstrate that a treat-to-target strategy using first-line monotherapy with rIL-1Ra is highly effective in patients with systemic JIA, for both short- and long-term outcomes. Patients with a normal neutrophil count at the start of rIL-1Ra treatment and/or an incomplete response after 1 month of therapy should be monitored closely, since they represent a group at risk of persistent disease activity.

DISCUSSION

The treat-to-target strategy using rIL-1Ra as first-line monotherapy for systemic JIA described herein resulted in rapid attainment of inactive disease, prevention of damage and functional limitations, and avoidance of glucocorticoids in the majority of patients. Furthermore, we demonstrated that inactive disease

while not receiving medication could be achieved in more than half of the patients within the first year of therapy.

The use of a biologic agent as first-line therapy is a paradigm shift compared to conventional step-up regimens used in systemic JIA. Although our study consisted of a single-center cohort without a formal control group, comparisons with previously published cohorts strongly suggest that our strategy is superior in achieving and sustaining inactive disease compared to conventional approaches. The percentage of patients with inactive disease after 1 year of therapy in our study was >2-fold higher than the percentages in other prospective trials using biologic agents as second- or third-line therapy in systemic JIA (17–20,34–36). Furthermore, the incidence of articular damage, growth failure, obesity, and functional limitations was ~3 times lower than in recent observational cohorts (21,22,37).

Since this was a single-center nonrandomized/controlled trial, a selection bias for less affected patients (for example, those with monocyclic disease) cannot be completely excluded. However, there are multiple arguments against a relevant selection bias for patients with a monocyclic or otherwise less severe disease course in our cohort. First, we included all consecutive patients with new-onset systemic JIA in our center over a prolonged period of time (9 years). Second, ~10% of the patients in our cohort experienced at least 1 episode of macrophage activation syndrome. This is consistent with rates of macrophage activation syndrome in other published cohorts and may be considered an indication of severe disease. Last, approximately half of the patients in our cohort had recurrent disease activity after the first attempt at tapering or cessation of rIL-1Ra. Hence, the results of our study confirm the high efficacy of first-line treatment of rIL-1Ra as described in a retrospective cohort (24), and support the existence of a so-called “window of opportunity,” favoring the initiation of biologic therapy early in the disease course (24,25).

An important aspect of our treat-to-target approach was to minimize exposure to glucocorticoids. The percentage of patients receiving glucocorticoids was reduced from 80–90% in previous cohorts to only 33% in our cohort, which is a major improvement given the well-known side effects of maintenance therapy with glucocorticoids (21–23,37,38). Since daily injections with rIL-1Ra pose a relevant burden to patients, it is important to consider tapering and stopping at an early time point (39). In our study, the median duration of rIL-1Ra treatment was only 6 months. However, since nearly half of the patients experienced recurrent disease activity after the first attempt to stop rIL-1Ra, future studies should try to identify and/or validate biomarkers of subclinical disease activity in order to optimize strategies for tapering and discontinuing biologic therapy in systemic JIA.

Our single-center, prospective cohort study may provide a first step toward personalized medicine for systemic JIA. The predictive value of neutrophil counts for response to rIL-1Ra supports findings from a previous study of our cohort, which provided evidence that neutrophils have an important role in the early inflammatory phase

of systemic JIA (40). Our findings suggest that, especially in the early phase of systemic JIA, which is characterized by pronounced innate immune activation and neutrophilia, patients may be highly responsive to IL-1 blockade, indicating the existence of a window of opportunity. Indeed, neutrophil counts were inversely correlated with disease duration in our patients. However, these observations may also reflect the heterogeneity of systemic JIA, with a systemic inflammatory phenotype on one end of the spectrum and an arthritis phenotype on the other. Longer (follow-up) and multicenter studies will help elucidate this point. Taken together, our data suggest that patients with systemic JIA with a normal neutrophil count at disease onset and at the start of rIL-1Ra treatment should be monitored closely for response. If systemic JIA symptoms, especially arthritis, persist despite 1 month of rIL-1Ra treatment, these patients may benefit from either the addition of (low-to-medium dose) prednisolone or a switch to another biologic agent.

Finally, a novelty of our study is the characterization and evaluation of patients in whom systemic JIA is suspected but who do not have arthritis at the initiation of treatment. It is well known that arthritis can develop months or even years after the first manifestation of systemic JIA symptoms (5,6). Waiting for the development of arthritis in these patients would result in therapeutic delay, which may increase the risk of nonresponse and development of damage. In this study, we showed that a treatment strategy using rIL-1Ra as first-line therapy is also highly efficacious in patients without arthritis at onset. Our results support consensus treatment plans from both American and German pediatric rheumatologists, stating that arthritis should not be a prerequisite for the initiation of biologic therapy (3,4), as well as the new suggested PRINTO classification criteria for systemic JIA, which omit the presence of arthritis as a prerequisite for the diagnosis of systemic JIA (33).

In conclusion, our treat-to-target approach in systemic JIA, using first-line monotherapy with rIL-1Ra, resulted in early and sustained inactive disease in the majority of systemic JIA patients, firmly reduced glucocorticoid use, and prevented the development of long-term disease- and therapy-related damage.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. ter Haar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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