Anakinra in Systemic Juvenile Idiopathic Arthritis: A Single-center Experience

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ABSTRACT. ***Objective.*** To assess anakinra as a therapy for systemic juvenile idiopathic arthritis (sJIA) in a single-center series.

Methods. We reviewed 25 patients with sJIA treated with anakinra for at least 6 months. The primary outcome was the number of patients who achieved clinically inactive disease at 6 months, according to preliminary criteria for inactive disease and clinical remission of JIA.

Results. Among 25 patients evaluated, 14 (56%) met the criteria for inactive disease at 6 months and were classified as responders. For each individual patient, we compared the dose administered with the ideal dose of anakinra and we found that there was no relation with response. We also compared demographic characteristics and clinical and laboratory features at baseline in responders and non-responders: no differences were observed in relation with the number of active joints before starting anakinra or concomitant glucocorticoids treatment. The only variable significantly associated with response was the time from disease onset to receiving anakinra, with earlier treatment being associated with a better outcome.

Conclusion. Anakinra is associated with rapid attainment of inactive disease in a significant portion of patients. We found that only the earlier treatment is associated with better outcome. However, formal studies on early treatment and on the pathophysiology and response to treatments, including anakinra, of early- and late-onset sJIA are needed to optimize the management of this challenging disease. (J Rheumatol First Release June 1 2015; doi:10.3899/jrheum.141567)

Key Indexing Terms:
SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS — ANAKINRA
CLINICAL INACTIVE DISEASE — DOSE ADMINISTERED

Systemic juvenile idiopathic arthritis (sJIA) accounts for 10–20% of all patients with JIA. The disease arises in both sexes in equal frequency and does not show preferential age at onset, with a broad peak between 1 and 5 years of age[1]. The clinical features include fever, rash, arthralgia and arthritis, myalgia, lymphadenopathy, hepatomegaly, splenomegaly, and serositis[2]. About half of patients with sJIA have a monocyclic course, or polycyclic course with flares separated by long periods of remission. In these patients, longterm outcome is usually good. The other half of patients have unremitting course with chronic persistent arthritis that may lead to joint destruction[1]. Standard treatments include high-dose glucocorticoids that cause significant side effects, including growth failure and osteoporosis[3]. Disease-modifying antirheumatic drugs (DMARD) and tumor necrosis factor inhibitors have limited efficacy in sJIA[4,5]. However, identification of the key role of the proinflammatory cytokines interleukin 1 (IL-1) and IL-6 resulted in the development of targeted therapeutic strategies[6,7,8] that are very efficacious in the short term and may lead to a significant change in the natural history of the disease.

Several reports, including 1 randomized clinical trial, reported that anakinra, the recombinant IL-1 receptor antagonist, is highly effective in a significant proportion of patients with sJIA, ranging from 30% to 60% in the different reports[6,9,10,11]. In some of these studies, better responses to anakinra have been associated to some clinical and laboratory features at baseline, including lower number of joints with active arthritis, higher absolute neutrophil count, and older age. Earlier treatment has also been suggested to be associated with better response. In a retrospective multicenter analysis of the use of anakinra in sJIA as first-line treatment, a high rate of complete response was reported[10]. Similarly in a prospective series of 20 patients consecutively diagnosed with sJIA, an 85% JIA American College of Rheumatology 90 response was reported[11]. In our study, we have retrospectively analyzed patients with sJIA treated with anakinra in our institution.

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MATERIALS AND METHODS

We conducted a retrospective single-center study in 25 patients with sJIA treated with anakinra for at least 6 months. The diagnosis of sJIA was established according to the International League of Associations for Rheumatology criteria[12]. We analyzed the effect of anakinra on fever, rash, number of active joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count, neutrophil cell count, platelet count, and hemoglobin and ferritin levels. The primary outcome was the number of patients who achieved clinically inactive disease at 6 months, according to the preliminary criteria for inactive disease and clinical remission of JIA[13]. According to these criteria, inactive disease is defined as absence of active arthritis and features that are specific for sJIA (i.e., absence of fever, rash, serositis, splenomegaly, and generalized lymphadenopathy), and normal ESR and CRP with physician's global assessment of disease activity indicating no disease activity.

Demographics, clinical, and laboratory data were collected from the division of rheumatology clinical database at baseline (before starting anakinra) and after 6 months of treatment with anakinra. Normal ranges used for laboratory data were as follows: CRP < 0.5 mg/dl, ESR < 15 mm/h, ferritin < 450 ng/ml, white blood cell count 5.500–15.000 × $10^3/\mu$l, neutrophil cell count 1.650–8.250 × $10^3/\mu$l, hemoglobin 10.5–15.5 g/dl, and platelet count 150–450 × $10^3/\mu$l.

Statistical analysis. Continuous variables were expressed as medians and interquartile ranges (IQR), and were compared using the Mann-Whitney U test. Proportions were compared using Fisher's exact test. In this analysis, p values less than 0.05 were considered significant. Variables significantly associated with clinical inactive disease at 6 months in univariate analysis were entered into a multivariate logistic regression analysis (STATA software, version 11).

RESULTS

Demographic, clinical, and laboratory features at baseline are shown in Table 1. We evaluated 25 patients (13 boys, 12 girls) with a median age at disease onset and at treatment start of 5.8 years (IQR 2.9–9.3) and 7.3 years (IQR 4.8–10.8), respectively. The median time from onset to receiving anakinra was 4.9 months (IQR 1.6–24.5). A great majority of patients had active systemic features at baseline, as shown by the presence of fever (92%), with most of them presenting also typical skin rash (76%). All patients had evidence of active joints, with the number ranging from 2 to 15 (median 3, IQR 2–7). Fourteen patients were receiving glucocorticoids (prednisone) at baseline with a median dose of 0.9 mg/kg (IQR 0.5–1.4). Of the 9 patients treated with DMARD, 6 were receiving methotrexate (MTX; dose ranging from 15 mg to 20 mg per m^2 of body surface area, once a week) and 3 were treated with oral cyclosporine (dose 5–6 mg/kg/day; Table 1). After 6 months of treatment, 14 patients (56%) met the criteria for inactive disease and were classified as responders. Inactive disease was reached at a median time of 2.1 months (IQR 1.3–3.5) after anakinra initiation. All of these 14 patients maintained clinically inactive disease at last visit (median followup duration 2.8 yrs, range 1.6–7.3), with 9 patients having been able to withdraw from anakinra and 5 continuing anakinra in monotherapy. Among the responders, the 6 patients receiving glucocorticoids at baseline were able to withdraw from this treatment (median time of withdrawal 2.7 mos). Among the nonresponders, 4 of the 8 patients receiving glucocorticoids at baseline were able to withdraw from them, with a mean dose of 0.04 mg/kg/day of prednisone in the remaining 4 patients. At last visit, the 3 responders receiving DMARD at baseline and at 6 and 12 months (MTX in 2 and cyclosporine in 1 patient) were able to withdraw completely from all treatments.

Table 1. Demographics and baseline characteristics of the 25 patients. Values are median (IQR) unless otherwise specified.

Characteristics	Values	ULN/LLN
Demographic features		
Female, n (%)	12 (48)	
Age at disease onset, yrs	5.8 (2.9–9.3)	
Age at treatment start, yrs	7.3 (4.8–10.8)	
MAS at disease onset, n (%)	7 (28)	
Baseline features		
Fever, n (%)	23 (92)	
Rash, n (%)	19 (76)	
No. active joints	3 (2–7)	
Concomitant glucocorticoids, n (%)	14 (56)	
Concomitant DMARD, n (%)*	9 (36)	
Previous biologics, n (%)**	6 (24)	
CRP, mg/dl	13.6 (8.6–15.8)	96% > ULN
ESR, mm/h	82 (65–100)	100% > ULN
Ferritin, ng/ml	719 (305.5–2875.5)	71% > ULN
WBC count, × $10^3/\mu$l	14.7 (8.2–20.3)	52% > ULN
Neutrophil cell count, × $10^3/\mu$l	10.5 (6.0–15.5)	52% > ULN
Hemoglobin, g/dl	10.7 (9.5–11.1)	80% > LLN
Platelet count, × $10^3/\mu$l	427 (384–610)	40% > ULN
Time from onset to receiving anakinra, mos	4.9 (1.6–24.5)	
Anakinra dose, mg/kg/day	2.0 (1.3–2.0)	
Anakinra dose ratio administered/ideal†	1.3 (0.9–1.7)	
Outcome		
No. patients with inactive disease at 6 mos from the beginning of the therapy, n (%)	14 (56)	

* Included 6 methotrexate and 3 cyclosporine. ** Included 4 etanercept; 1 etanercept and abatacept; 1 etanercept and infliximab. † Ideal as predicted by Figure 4 of Urien, *et al*[14]. IQR: interquartile range; MAS: macrophage activation syndrome; DMARD: disease-modifying antirheumatic drugs; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell; ULN: upper limit of normal; LLN: lower limit of normal.

No major adverse events were recorded in our series with the exception of 2 patients who reported injection site reactions that did not require discontinuation of treatment. Among the 25 patients, there were no cases of macrophage activation syndrome (MAS) during the treatment with anakinra. Four patients (16%) had MAS at presentation of sJIA; in 2, we successfully used anakinra as the initial therapy without systemic glucocorticoids. Three patients (12%) had MAS some years before starting anakinra and no MAS was observed during anakinra treatment in these patients.

To evaluate whether the response to anakinra might be related to the dose administered, we analyzed in our patients the median starting dose and the subsequent increase. The median starting dose of anakinra was 2 (IQR 1.3–2.0) mg/kg/day and subsequent dose escalation was required in

20% of patients (maximum dose 5 mg/kg/day). There was no difference in the median starting dose and in the number of patients who escalated between responders and nonresponders (Table 2). Other studies pointed to the need for higher anakinra dosage in low-weight children[6]. The only pharmacokinetic study of anakinra in children demonstrated higher clearance in lower weight children and derived appropriate dosing ranges according to body weight (BW)[14]. They proposed a dosage of 2 mg/kg/day for patients with BW from 10 kg to 50 kg, a dosage of 3 mg/kg/day for patients with BW < 10 kg, and a dosage of 100 mg/kg/day for patients with > 50 kg BW[14]. Therefore, for each individual patient, we compared the dose administered with the ideal dose according to the plot by Urien, *et al*[14] (Figure 1). Although some of our patients were clearly underdosed, there was no relation with response (p = 0.956). Also, the ratio between the administered and the ideal doses was not different between responders and nonresponders (p = 0.721; Table 2).

Table 2. Relation of the response to anakinra and the dose administered and comparison between dose administered with the ideal dose. Values are median (IQR) unless otherwise specified.

Anakinra Study	Inactive Disease	Active Disease	p
Baseline anakinra dose, mg/kg/day	2.0 (1.2–2.1)	1.7 (1.4–2.0)	0.956*
No. patients in which dose was increased, n (%)	1 (7)	4 (36)	0.133**
Anakinra dose ratio administered/ideal, n (%)†	1.3 (1.0–1.7)	1.3 (0.9–1.6)	0.721*

* Mann-Whitney U test. ** Fisher's exact test. † Ideal as predicted by Figure 4 of Urien, *et al*[14]. IQR: interquartile range.

Because in this series anakinra dose was not associated with the response, we compared demographic characteristics and clinical and laboratory features at baseline in responders and nonresponders. As shown in Table 3, there was no significant difference between the 2 groups in demographic, clinical, and laboratory features. In a multivariate analysis, none of these variables was significantly associated. In particular, no differences were found in the number of active joints before starting anakinra or concomitant glucocorticoids treatment. In our study, we found that at onset of disease, nonresponders were younger (median 3.3 vs 7.4 yrs) and responders had higher ferritin levels (median 1506 vs 360 ng/ml); however, these differences were not significant (p = 0.090 and p = 0.079, respectively). The only variable significantly associated with response was the time from disease onset to receiving anakinra, with earlier treatment being associated with a better outcome (p = 0.003). In a logistic regression approach that included the variables with a p value < 0.1 in a univariate analysis, we did not find any significant association with response.

DISCUSSION

In our study, we report a single-center experience with the use of anakinra in sJIA. In agreement with other studies, we found that treatment with anakinra is associated with rapid attainment of inactive disease in a significant portion of patients (56% in this series). Incidentally, no major adverse

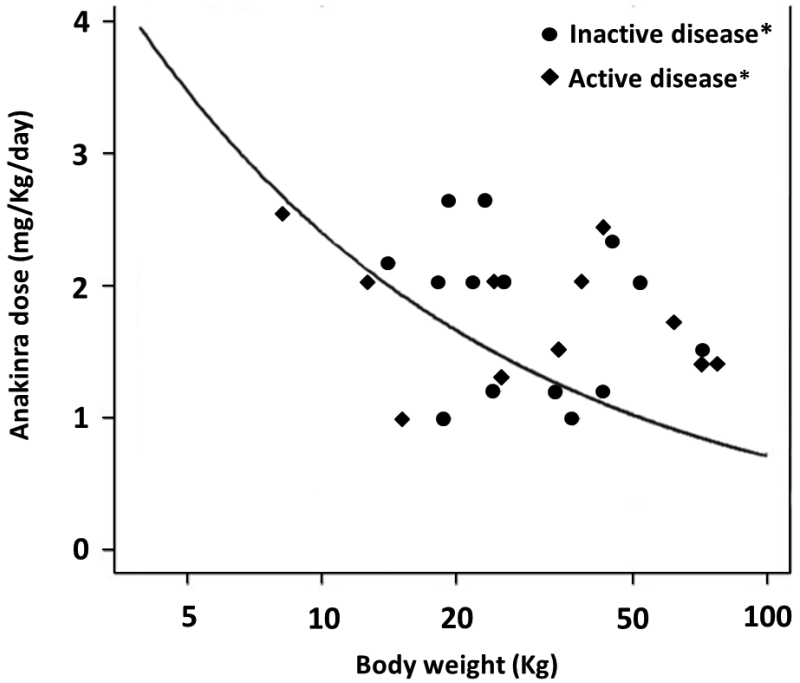

Figure 1. Comparison for each individual patient between the dose of anakinra administered with the ideal dose, according to the plot by Urien, *et al*[14], BMC Pharmacol Toxicol 2013;14:40; adapted with permission. *After 6 months of anakinra therapy.

Table 3. Univariate analysis for predictors of clinically inactive disease of 6 months. Values are median (IQR) unless otherwise specified.

Anakinra Study	Inactive Disease	Active Disease	p
Patients, n (%)	14 (56)	11 (44)	
Female, n (%)	6 (43)	6 (55)	1.0**
Age at disease onset, yrs	7.4 (4.8–9.7)	3.3 (2.0–6.2)	0.090†
Age of treatment start, yrs	7.9 (4.9–9.9)	6.2 (4.4–12.5)	0.891†
MAS at disease onset, n (%)	4 (29)	3 (27)	1.0**
Time from onset to receiving anakinra, mos	1.9 (0.8–5.4)	24.5 (6.2–58.4)	0.003†*
Concomitant glucocorticoids, n (%)	6 (43)	8 (73)	0.227**
Concomitant DMARD, n (%)	3 (21)	6 (55)	0.115**
Fever, > 38.0°C , n (%)	14 (100)	9 (82)	0.183**
Rash, n (%)	13 (93)	6 (55)	0.056**
No. active joints	3 (2–4.5)	4 (2–12)	0.160†
ESR, mm/h	76 (65.3–88.8)	90 (66.5–106.5)	0.460†
CRP, mg/dl	13.4 (9.7–15.7)	13.6 (6.6–18.4)	0.870†
Ferritin, ng/ml	1506 (407–3520)	360 (177–1915)	0.079†
WBC count, × mm^3	15.5 (8.6–23.3)	12.8 (8.4–18.7)	0.298†
Neutrophil count, × mm^3	12.6 (6.4–16.5)	7.4 (5.9–14.4)	0.324†
Hemoglobin, g/dl	10.6 (9.4–11.1)	10.8 (10–11.5)	0.493†
Platelet count, × mm^3	416.5 (385.3–638.5)	427 (378.5–590)	0.827†

* $p < 0.05$. ** Fisher's exact test. † Mann-Whitney U test. IQR: interquartile range; MAS: macrophage activation syndrome; DMARD: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell.

events were recorded with the exception of some cases of injection site reactions that did not require discontinuation of treatment. We used inactive disease as the primary outcome because we wanted to identify patients with a prompt and complete response to the treatment with anakinra. This is an ambitious but reachable objective, particularly in patients treated early in the disease course.

Our results do not support the conclusion that the dose of anakinra administered was associated with response. Given the general knowledge that younger children require higher dosages, this consideration has always been put forward when interpreting data on the clinical efficacy of anakinra over a wide age range. We compared the dose administered with the ideal dose as predicted by the pharmacokinetics of anakinra[14], and used the ratio between the 2 as a measure of an appropriate dosing of each individual patient. Although some of our patients were underdosed based on this analysis, this was not associated with response. It should be noted that such an analysis has not been performed in previous reports on patients with sJIA treated with anakinra. Dosing based on BW must be driven by the available pharmacokinetic data. However, this approach does not rule out the possibility that some individual patients might require higher doses; and this is not addressed in our study.

We also evaluated whether baseline variables predicted future response. The only variable significantly associated with response was the time from disease onset to receiving anakinra, with earlier treatment being associated with a better outcome. Other variables loosely associated with better response were older age at onset of sJIA, high ferritin levels, and presence of skin rash at baseline. However, in a multivariate approach, none of these were significantly associated, possibly because of the small number of patients. Incidentally, number of active joints at baseline and neutrophil count were not associated with clinically inactive disease at 6 months, in contrast to what was reported by Gattorno, *et al*[15].

Our results regarding early treatment are consistent with those reported by Nigrovic, *et al* and Vastert, *et al*[10,11]. All together, these results may suggest a better response to anakinra if used early in the disease course, and are indeed consistent with the hypothesis[16] of a window of opportunity in which patients are more responsive to IL-1 inhibition. However, because up to 50% of patients with sJIA naturally have a monocyclic course with spontaneous remission, results of open studies on patients with early disease, including ours, may be biased by the inclusion of a variable percentage (up to 50%) of patients with natural monocyclic disease. Therefore, the hypothesis of a window of opportunity is far from proven, and should represent the focus of further research into the pathophysiology of sJIA and ideally be the objective of future multicenter trials in larger populations, possibly coupled with biomarker studies.

Our data suggest that older age at onset of sJIA may be associated with a better response. Interestingly, in their retrospective collection, Nigrovic, *et al* also reported a statistically significant difference in the age at onset of sJIA between responders and partial or nonresponders (median 10.2 yrs vs 5.2 yrs, respectively)[10], and this was the only variable significantly associated with response. It was hypothesized that

suboptimal anakinra dosage could be a potential explanation for poorer responses in younger children. However, this hypothesis was not formally investigated. As mentioned, in our study we did not find a relationship between underdosing and response. It is also noteworthy that in the study by Gattorno, *et al*[15], complete responders had a higher median age than nonresponders (8.3 yrs vs 4.6 yrs, respectively). No information on age at onset is provided in the paper by Vastert, *et al*[11]. This potential difference in response to IL-1 inhibition needs to be studied in a large population. Indeed, early-onset sJIA has been described as significantly more severe, particularly if onset occurs before 18 months of age[17]. It has been hypothesized that patients with a very favorable response to anakinra may represent a subset of the disease, possibly very similar to the adult disease at present called adult-onset Still's disease, in which an autoinflammatory component may be particularly relevant[18]. It is tempting to speculate that the disease with late-onset age may represent a separate entity from that with early onset, with a potential difference in the underlying pathogenic mechanisms. Again, this hypothesis needs to be formally studied.

Our data add to the already existing open-label reports further confirming the efficacy of anakinra in a sizeable percent of patients. However, formal studies on early treatment and on the pathophysiology and response to treatments, including anakinra, of early- and late-onset sJIA are needed to optimize the management of this challenging disease.

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