ARP Rheumatology 2024;3:288-294
https://doi.org/10.63032/TEVI1838

ORIGINAL ARTICLES

Anakinra as a first-line therapy for systemic juvenile idiopathic arthritis when nonsteroidal anti-inflammatory drug treatment fails: a single-center French retrospective study

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ABSTRACT

Introduction: Anakinra has dramatically improved the management of systemic juvenile idiopathic arthritis (SJIA) over the last decade. Nevertheless, management remains inconsistent; corticosteroids are still frequently used. We analyzed the course of SJIA in children treated with anakinra according to the time of treatment initiation after disease onset.

Methods: Children with SJIA treated with anakinra between 2006 and 2020 were included in this single-center, retrospective observational study.

Results: Twenty-four children received anakinra at a median time of 58 (range 12–2940) days after SJIA onset, all after failure of nonsteroidal anti-inflammatory drug (NSAID) treatment. Eighteen were males and the median age at disease onset was 6.04 (range 0.8–13) years. The median follow-up time was 3.5 (range 0.5–10.8) years after treatment initiation. At the last follow-up, remission attributable to anakinra was observed in 18/24 (75%) children and treatment-free remission was observed in 12 (67%). For each child, the response to anakinra was the same at 3 months and at the last follow-up. The 15 children treated with anakinra within the first 3 months after disease onset exhibited better remission (93%) than did the 9 children treated after 3 months (44%) ($p = 0.015$) and the former received fewer corticosteroids (7% versus 67%) ($p = 0.004$). One child with long-standing disease died of the disease.

Conclusions: Early anakinra initiation within the first 3 months of SJIA onset after NSAID failure ensures long-term remission and reduces corticosteroid use. Anakinra should not be continued for more than 3 months in nonresponding children.

Keywords: Children; Systemic juvenile idiopathic arthritis; Interleukin-1; Window of opportunity; Anakinra.

KEY MESSAGES

- Early anakinra initiation within the first 3 months after SJIA onset rapidly induces long-term remission and reduces corticosteroids use.
- Anakinra should not be continued for more than 3 months in nonresponding children.

INTRODUCTION

Systemic juvenile idiopathic arthritis (SJIA) constitutes 10–20% of all juvenile idiopathic arthritis (JIA)[1]. SJIA diagnosis is based on the new EULAR/PReS 2024 classification criteria[2]. According to these new recommendations, SJIA and adult-onset Still's disease are the same disease, that should be designated by the same unique name, Still's disease. Criteria for Still's disease include a spiking fever for at least 7 days, a transient macular erythematous rash, arthralgia or arthritis, and a significant biological inflammatory response characterized by neutrophilic leukocytosis, and elevated C-reactive protein (CRP) and ferritin levels[2].

In contrast to the other subtypes of JIA, SJIA is an autoinflammatory rather than an autoimmune disease, characterized by systemic manifestations. There is an immunologic continuum in SJIA, the innate immune system response predominates at the initial phase of

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Submitted: 25/09/2024
Accepted: 05/12/2024

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the disease, whereas the adaptative response is more implicated in the latter one[2–4]. Several inflammation molecules appear to be involved in the initial phase of the disease: interleukin (IL)-1, IL-6, IL-18 and interferon γ[2]. Among them, dysregulation of (strongly pro-inflammatory) IL-1 synthesis seems to predominate in the initial phase of disease[3,5].

The SJIA course is very variable. Of all affected children, 40–50% exhibit monocyclic or polycyclic disease[6]. The others commonly progress to persistent joint involvement; the systemic manifestations tend to disappear[6]. SJIA is associated with the poorest prognosis of all forms of JIA given that it is associated with acute complications such as macrophagic activation syndrome (MAS), cardiac and lung involvements, and infections as well as chronic complications such as growth retardation, joint destruction, osteoporosis attributable to prolonged corticosteroid (CS) use, and amyloidosis[7–9].

The first-line treatments for SJIA are nonsteroidal anti-inflammatory drugs (NSAIDs). However, the second-line drugs vary, and include CSs, disease-modifying anti-rheumatic drugs (DMARDs), and biologic therapies[10–12]. The key role played by IL-1 in early-stage disease has encouraged the use of IL-1-blocking treatments over the last decade. The responses to SJIA treatment have improved dramatically in recent years after the development of IL-1 receptor antagonists (IL-1Ras) such as anakinra[12–15], although some patients do not respond[16]. More recently, some studies have highlighted the utility of anakinra as a first-line treatment; rapid remission is apparent in most children who thus need fewer CSs[17–20]. According to the new EULAR/PReS 2024 recommendations, due to their efficacy and safety profiles and their CS sparing effect, an IL-1 (anakinra, canakinumab, and rilonacept) or IL-6 (tocilizumab) inhibitor should be initiate as early as possible when the diagnosis is established[2]. Together, the data support IL-1 or IL-6 inhibitors prescription early in the disease; this is the "window of opportunity"[21]. However, low-level evidence suggest that IL-1 and IL-6 inhibitors should be initiated before 3 months from symptoms onset[2], and CSs continue to be prescribed for more than half of all affected children[11].

The ultimate goal of this treatment to target strategy is drug-free remission. Maintenance of inactive disease for 3–6 months without CSs should be achieved before initiating progressive treatment tapering stepwise by steps of 3–6 months, preferentially by injection interval prolongation[2].

Among the IL-1 inhibitors, anakinra appears to have the most reassuring safety profile and its short half-life enables rapid elimination in the event of a diagnostic error. In the case of MAS, treatments other than IL-1 and IL-6 inhibitors should be considered: high dose CSs, ciclosporin, interferon γ inhibitors, JAK inhibitors and low-dose etoposide[2].

We retrospectively analyzed the courses of SJIA children treated with anakinra in our French, tertiary, pediatric rheumatology center, by the time at which anakinra therapy commenced after disease onset.

MATERIALS AND METHODS

Population

Children with SJIA prescribed anakinra, with or without CSs, treated at the University Hospital of Bordeaux, France, between January 2006 and August 2020 were retrospectively included. The diagnosis of SJIA was confirmed by a pediatric rheumatologist. The study was conducted under the French data protection authority MR004 reference methodology, and was declared to local ethical committee.

Data collection

We retrospectively reviewed computerized medical records and extracted age at disease onset; sex; all systemic signs (fever, lymphadenopathy, rash, fatigue, hepatomegaly, splenomegaly, serositis, and lung involvement); MAS status; the number of affected joints; biological data; the prescribed drugs; drug doses; and the times from disease onset to drug prescriptions. All follow-up data during visits after anakinra prescription were recorded.

Outcomes

Early anakinra treatment was defined as anakinra prescription within 3 months of disease onset[22]. Clinical inactive disease (CID) was defined as absence of Still's disease-related symptoms and normal erythrocyte sedimentation rate (ESR) or CRP, and remission was defined as a period of at least 6 months with CID[2]. Anakinra-attributable CID and remission were defined as CID and remission on only anakinra, thus without CSs or DMARDs. Remission-off treatments, was defined as persistence of remission for more than 3 months after discontinuation of all treatment.

Statistical analyses

Data were entered into Excel ver. 2008. Descriptive statistics such as means, frequencies, and standard deviations are presented as appropriate. We compared continuous and categorical variables using the non-parametric Wilcoxon or Mann-Whitney test, or the Fisher exact test, respectively. All tests were two-sided and the significance level was set to $p < 0.05$.

RESULTS

Population and manifestations at disease onset

Twenty-four SJIA children were consecutively prescribed anakinra in the University Hospital of Bordeaux between 2006 and 2020. Eighteen (75%) were males. The median age at symptom onset was 6.04 (range 0.8–13) years and the median time from symptom onset to SJIA diagnosis was 30 (range 5–365) days. The median follow-up time after anakinra commencement was 3.5 (range 0.5–10.8) years.

The clinical and biological characteristics at disease onset are detailed in Table I. All children presented with fever and fatigue, and 22 (92%) had a rash. Twenty (83%) children evidenced arthritis and the remaining four (17%) had arthralgia but without arthritis. The number of affected joints ranged from 1 to 27. Pericarditis was apparent in trans-thoracic ultrasound in eight (33%) children, pleuritis in six (25%) and MAS in three (13%). All children had an elevated CRP.

TABLE I. Characteristics of the 24 children with systemic juvenile idiopathic arthritis.

Demographic features	
Male/female	18/6
Age at symptom onset; median (min-max) years	6.04 (0.8–13.00)
Clinical features, n (%)	
Fever	24 (100%)
Fatigue	24 (100%)
Rash	22 (92%)
Arthritis	20 (83%)
Lymphadenopathy	15 (63%)
Hepatomegaly or splenomegaly	5 (21%)
Serositis (pericarditis and/or pleural effusion)	12 (50%)
Macrophage activation syndrome	3 (13%)
Laboratory parameter at diagnosis, median (min-max)	
Hemoglobin level, g/dL	9.3 (6.6–13.1)
White blood cell count, 10^9/L	24.25 (11.6–34.9)
Absolute neutrophil count, 10^9/L	19.46 (7.1–26.5)
Platelet count, 10^9/L	532.5 (140–729)
C-reactive protein (CRP), mg/L	168.5 (21–459)
Ferritin, ng/mL	2011 (130–28293)
Aspartate aminotransferase (ASAT), U/L	32.5 (18–1328)

Treatments before anakinra initiation

All children received NSAIDs for a mean duration of 28 (range 5–245) days, but NSAIDs did not allow CID in all patients. Thirteen (54%) were subsequently prescribed different NSAIDs. Five children received another drug after NSAID failure but before anakinra initiation: CS (n = 5), methotrexate (n = 1), and etanercept (n = 1). All these children were diagnosed before 2010 and received anakinra > 3 months after disease onset. The persistence of active disease in such children led to anakinra initiation.

Disease course by the time of anakinra initiation

Anakinra was introduced at a median of 37 (range 5–1460) days after NSAID prescription and 58 (range 12–2940) days after disease onset. The initial dose was 2 (range 1.9 to 2.5) mg/kg/day. After 1 and 3 months, CID was obtained in 13/24 (54%) and 18/24 (75%) children, respectively. The latter remained in anakinra-attributable remission at their last follow-up visits. None of the six children not in CID after 3 months of anakinra were in anakinra-attributable remission at the end of follow-up. Of children in remission attributable to anakinra, treatment-free remission was observed in 12/18 (67%) at the last follow-up, and anakinra was discontinued at a median time of 18.5 (range 7–36) months.

Anakinra was initiated during the first 3 months of disease (i.e., early) in 15/24 (63%) children, and after 3 months (i.e., late) in 9/24 (37%) in a median delay of 7 (range 3.3-98) months after disease onset. Children that were treated with anakinra early were older than others at disease onset, evidenced a shorter diagnostic delay, and had a higher white blood cell count and neutrophil and ferritin levels (Table II). These children achieved significantly more remission attributable to anakinra (14/15 = 93%) than did those in the late group (4/9 = 44%) (p = 0.015, odds ratio [OR] 15.1, 95% confidence interval [CI] [1.22; 878.68]). For the four children in the late group who achieved remission attributable to anakinra, the drug was initiated at a median of 5.4 (3.5–8.2) months after disease onset. The disease courses at the last follow-up by the early or late introduction of anakinra are detailed in Figure 1.

One child in the early group who did not achieve remission attributable to anakinra finally entered remission after anakinra was replaced by canakinumab at 18 months. Of the five children in the late group who did not achieve remission attributable to anakinra, four entered remission after replacement of anakinra: one was changed to canakinumab after 12 months and 3 to tocilizumab after 3 months, 3 years, and 3.2 years of anakinra, respectively. At the last follow-ups, remission regardless of treatment was observed in 23/24 (96%) children. The remaining child died; he had long-standing disease and failed several lines of therapy before anakinra initiation. Death was not at-

TABLE II. Characteristics of the 24 children with systemic juvenile idiopathic arthritis by early or late anakinra initiation status.

	Early anakinra n = 15	Late anakinra n = 9	p-value
Demographic features			
Male/female	13/2	5/4	0.15
Age at symptom onset, median (min-max); years	7.9 (1.1–13)	2.7 (0.8–9.8)	**0.02**
Disease onset before 2010, n (%)	2 (13%)	5 (56%)	0.06
Time from onset to diagnosis; median (min-max) days	18 (5–66)	88 (33–365)	**<0.01**
Clinical features at diagnosis, n (%)			
Fever	15 (100%)	9 (100%)	1
Fatigue	15 (100%)	9 (100%)	1
Rash	13 (87%)	9 (100%)	0.51
Arthritis	11 (73%)	9 (100%)	0.26
Lymphadenopathy	10 (67%)	5 (56%)	0.68
Hepatomegaly or splenomegaly	2 (13%)	3 (33%)	0.33
Serositis	6 (40%)	6 (67%)	0.40
Macrophage activation syndrome	2 (13%)	1 (11%)	1
Laboratory parameters at diagnosis, median (min-max)			
Hemoglobin level, g/dL	9.1 (6.6–12.2)	10.1 (7–13.1)	0.27
White blood count, 10^9/L	26.1 (17.6–34.9)	19 (11.6–30.8)	**0.02**
Absolute neutrophil count, 10^9/L	22.3 (13.8–26.5)	10.1 (7.1–22.3)	**<0.01**
C-reactive protein (CRP), mg/L	178 (75–459)	114 (21–252)	0.12
Ferritin, ng/mL	2840 (130–28293)	1163 (279–12014)	**0.04**
Remission attributable to anakinra, n (%)	14 (93%)	4 (44%)	**0.02**
Use of corticosteroids, n (%)	1 (7%)	6 (67%)	**<0.01**
Follow-up time, median (min-max) years	3.1 (2–9.8)	3.9 (0.5–10.8)	0.16

tributable to anakinra. The autopsy revealed chronic myocarditis, pericarditis, and pleural damage.

CSs were added for brief periods after anakinra initiation in two children, one from either group. In summary, CSs were ultimately employed in 7/24 (29%) children: 1/15 (7%) of the early group and 6/9 (67%) of the late group (p = 0.004, OR 22.9, 95% CI [1.87; 1360]).

Adverse events attributable to anakinra

The main adverse events were infections and injection site reactions. Bacterial ear, nose, and throat infections occurred in 8/24 (33%) children, ranging from simple tonsillitis to acute mastoiditis. All resolved after transient suspension of anakinra for a median of 6 (range 1–12) days. Gastritis caused by *Campylobacter jejuni* was observed in one child. Injection site reactions occurred in 3/24 (12.5%) children but did not require treatment discontinuation. One child exhibited transient elevations of liver enzyme levels requiring brief 7-day suspension of anakinra; then the levels normalized.

DISCUSSION

We report our single-center, real-world experience of early use of anakinra to treat SJIA when NSAIDs fail. Although our study was both retrospective and had a small sample size, we confirm that early use of anakinra (within the first 3 months after SJIA onset) rapidly renders the disease inactive, and this response is prolonged; and reduce the CSs used. The CID, remission, and treatment-free remission rates of our work are consistent with those of previous studies with similar follow-up times[17–19,23].

Nigrovic et al. (2011) were the first to suggest the efficacy of first-line anakinra therapy in 46 children with SJIA[17]. Most patients also received CSs and/or DMARDs[17]. Nigrovic later opined that SJIA was biphasic where by the initial phase was mediated by innate immunity and the later phase was mediated by adaptive immunity; thus, there was a therapeutic "window of opportunity"[21]. Indeed, the early phase is characterized by systemic manifestations that reflect principally IL-1 production; IL-1 blockade may induce prolonged

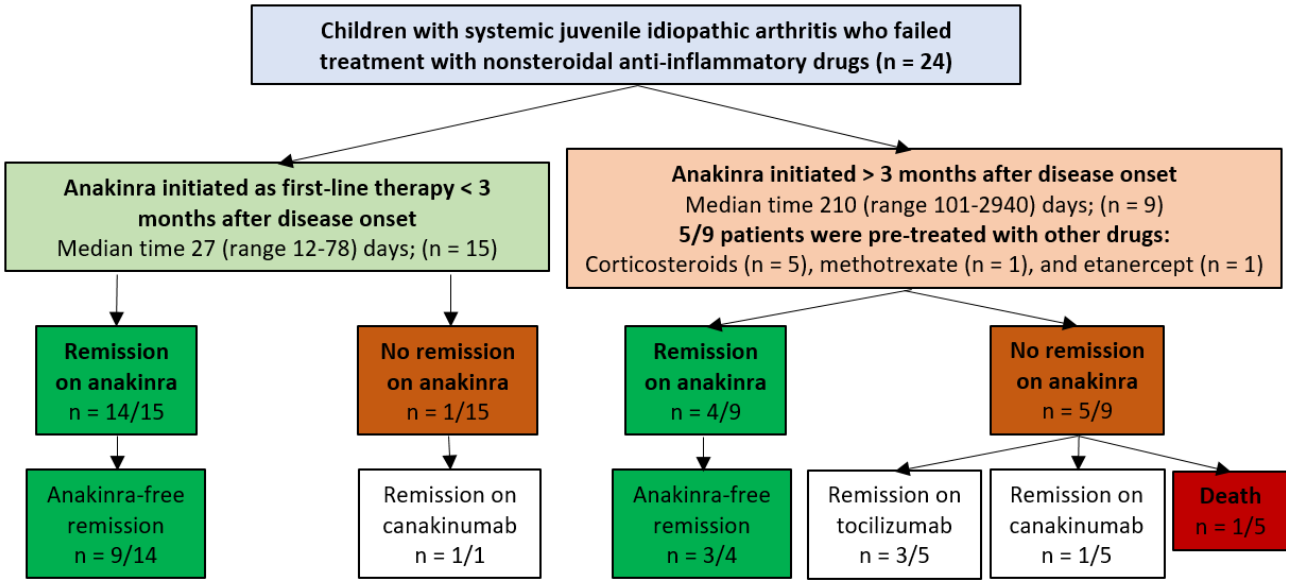

Figure 1. Disease status at the last follow-up by early (<3 months) or late (>3 months) anakinra prescription after disease onset.

control of inflammation and improve the long-term outcome[21]. This hypothesis is difficult to prove; almost half of SJIA patients exhibit a monocyclic course with spontaneous remission over time[24]. However, several later studies support anakinra first-line therapy[18,19]. By contrast, Vitale et al. observed no correlation between the time of anakinra introduction and disease outcome in a retrospective study on 141 adult patients with Still's disease[25]. In Pardeo et al., who enrolled 56 SJIA children, the 6-month response to anakinra was related to the time of anakinra initiation from disease onset; the optimal timing was 3 months. Patients who commenced on anakinra ≥ 3 months after disease onset were at an 8-fold increased risk of nonresponse after 6 months of treatment[22]. According to the new EULAR/PReS 2024 recommendations, due to their efficacy and safety profile and their CS sparing effect, an IL-1or IL-6 inhibitor should be initiate as early as possible. This step-up approach is part of a global treatment to target strategy, the ultimate goal of which is drug-free remission obtained with rapid step-down approach when CID is achieved. However, low-level evidence suggest that IL-1 and IL-6 inhibitors should be initiated before 3 months from symptoms onset[2]. Our study offers further evidence that anakinra efficiently treats SJIA when given in the therapeutic window of opportunity, thus within 3 months after disease onset, as a first-line therapy when NSAIDs fail.

Strengthening the evidence base on the benefits afforded by early anakinra initiation in SJIA children is important, as management remains heterogeneous and CSs are too often employed[11]. Peterson et al. suggested that anakinra first-line therapy would reduce CS exposure and thus the adverse effects of prolonged CS use in SJIA patients[26]. In prospective study of Ter Haar et al. on 42 SJIA children, the use of anakinra as first-line therapy reduced the use of CSs to only one-third of patients[19]. In our study, concomitant with anakinra or prior CS use was noted in slightly less than one-third of the children. Moreover, early anakinra treatment reduced the need for CS to only 1/15 children. Similarly, two previous studies found that early anakinra initiation was followed by remission in most steroid-naïve children with SJIA; CSs were not required[17,18]. However, in a recent study conducted from 2008 to 2019 on 534 children with SJIA treated in 52 tertiary children's hospitals, 58% received CSs; and CS use remained unchanged over time while biologic use increased[11], highlighting the need to reduce real-world CS exposure.

Notably, we found that, for all children, the responses to anakinra were the same at 3 months and the last follow-up. All children in anakinra-attributable remission at the last follow-up had exhibited CID after 3 months of anakinra. Conversely, no child in whom disease remained active after 3 months on anakinra was in anakinra-attributable remission at the last follow-up. Two previous studies also observed that almost all children in anakinra-attributable remission at the last follow-up were already in remission after 3 months of treatment[18,19]. Such data may indicate that anakinra need not be continued after 3 months if the disease remains active.

We cannot assert that anakinra efficacy was entirely attributable to the time of drug commencement; our

two groups differed somewhat. Children in the early group were older at disease onset, were diagnosed more rapidly, and had a higher white blood count, and neutrophil and ferritin levels. Older children seem to respond better to anakinra than do younger children[16,17,27]. In Nigrovic et al., child responders were older (median age 10.2 years) than non-responders (median age 5.2 years)[17]. By contrast, Ter Haar et al. observed that the best responders were the youngest[19]. An association between an inflammatory syndrome and the response to anakinra has been suggested in several studies. A high ferritin level was associated with a response to anakinra in some studies but not others but a high neutrophil count was associated with a response in most studies[16,17,19,28]. As mentioned above, the early phase of the disease (during which anakinra appears to be most effective) is characterized by a highly pro-inflammatory state associated with IL-1 production[3–5,21]. This may explain why patients in the early group exhibited a more pronounced inflammatory syndrome at diagnosis; since they were diagnosed earlier and therefore received anakinra earlier. Certain other factors may influence the response to anakinra; its prescription prior to arthritis onset seemed to correlate with better outcomes in some studies[17,19,28]. However, Pardeo et al. found that active arthritis status did not affect attainment of remission on anakinra[27]. A genetic contribution to the anakinra response has also been suggested; certain IL1 receptor variants may influence the response in SJIA patients[22,29], although one study suggested otherwise[30]. Identification of possible anakinra response determinants such as IL1-RN single-nucleotide polymorphisms would aid a personalized approach to treatment.

We found that anakinra was well-tolerated. The only death was attributable to uncontrolled disease, not to anakinra. Infections, mainly those of the ear, nose, and throat, were the most common side effects, as in most previous studies[14,15,17,18]. No infection was severe; anakinra was suspended only briefly. In contrast to most biologics, which are monoclonal antibodies, anakinra has a short half-life and thus is rapidly eliminated when a side effect requires its immediate discontinuation. Transient reactions at the injection site were observed, but never required treatment discontinuation. This nonsevere local side effect has also been frequently reported[14,15,18]. Hepatitis attributable to anakinra has also been noted in 3 children; anakinra permanent suspension was required in 1/3 children[31]. Overall, in the large German studies of the AID and BIKER registries, the safety profile of anakinra was acceptable[20,23,32].

Anakinra is effective, acceptably safe, and cost-effective. In one recent study, the 5-year cost of first-line anakinra treatment was lower than that of second-line treatment (€43,218 versus €45,896). Although first-line anakinra is more expensive than other drugs, medical resource use and hospital days decrease[33].

CONCLUSION

This retrospective, single-center, real-world study confirms that early anakinra use (within the first 3 months after SJIA onset) when NSAIDs fail rapidly induces long-term inactive disease; and reduces CSs use. Anakinra should not be continued for more than 3 months in non-responders. Further studies should seek factors associated with a response to anakinra; this would guide anakinra use in SJIA patients.

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