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ORIGINAL RESEARCH article

Anakinra treatment for systemic onset juvenile idiopathic arthritis in Libyan Children

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Abstract: Systemic onset juvenile idiopathic arthritis (SoJIA) is a rare inflammatory disorder. It is the severest form of juvenile idiopathic arthritis, and complications occur most commonly in this type. Non-responsiveness to standard therapy with corticosteroids and disease-modifying antirheumatic drugs is not uncommon. Interleukin-1 beta (Il-1β) has been shown to be a main contributor to the pathogenesis of SoJIA. Anakinra, a recombinant Il-1β receptor antagonist, was shown to be effective in small cohorts of therapy-resistant adult and pediatric still's patients. This study aimed to evaluate the real-world efficacy, steroid-sparing effect, and safety profile of anakinra in patients with SoJIA at a tertiary care center in Libya. A retrospective case series was conducted on patients with SoJIA treated with anakinra at the Tripoli Children's Hospital between 2010 and 2017. Data on demographic characteristics, disease activity, corticosteroid dosage, concomitant medications, and adverse events were collected at baseline and at 1-, 3-, 6-, and 12-month post-treatment. 13 patients were treated with anakinra with a mean age of 9.4±4.6 years at anakinra initiation and a female-to-male ratio of 2: 1. All patients were on corticosteroids and 92.3% on methotrexate at treatment initiation. The proportion of patients achieving inactive disease (Jadas 10=0) increased over time. A marked steroid-sparing effect was observed: the number of patients requiring high-dose steroids (>0.5 mg/kg/day) decreased from 100% at baseline to 7.6% at 12 months, and 53.8% successfully discontinued corticosteroids entirely. All patients experienced injection site reaction, and macrophage activation syndrome occurred in 15.4% as a side effect after treatment initiation. But no severe infections or fatalities occurred. Reasons for discontinuation included remission (46.1%), drug unavailability (23.0%), inefficacy (15.3%), and side effects (15.3%). Anakinra demonstrated significant efficacy in inducing rapid disease control and reducing corticosteroid dependence in patients with refractory SoJIA, with a manageable safety profile.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory joint disease with onset in children [3]. JIA is a heterogeneous disease that contains seven diverse categories in the systemic JIA (SoJIA) category. Classification of JIA based on presence of arthritis and of a documented quotidian fever of two weeks' duration; Plus, typical rash, generalized lymph-adenopathy, enlargement of liver or spleen, or serositis [4]. Systemic

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arthritis is one of the most perplexing diseases of childhood. Its onset can be quite nonspecific and may suggest bacterial or viral infection, malignancy, or another inflammatory disease; it is an important element in the differential diagnosis of fever of unknown origin [5]. Chronic arthritis develops in patients with systemic JIA and can be resistant to conventional disease-modifying antirheumatic drugs (DMARDs), as methotrexate (MTX) and tumor necrosis factor inhibitors [6]. SoJIA is the single potentially life-threatening form of JIA; it is the form of JIA frequently associated with significant internal organ involvement [5]. SoJIA is considered to have a different etiology compared with other forms of JIA; it is more auto-inflammatory in nature [3, 7]. Children with SoJIA are usually very Ill at the time the diagnosis is made. The characteristic clinical presentation of SoJIA is the child with greater than six weeks of intermittent fever, rash, and arthritis [5]. Sustained high fevers in a patient with suspected SJIA should alert the clinician to the possibility of macrophage activation syndrome (MAS), which can occur at disease onset [8]. Additional complications of SoJIA include osteopenia, growth retardation, erosive arthritis, and amyloidosis, MAS [9]. This is a serious, life-threatening complication characterized by unremitting high fever, pancytopenia, hepatosplenomegaly, hepatic dysfunction, encephalopathy, and coagulation abnormalities [5]. Laboratory examination indicators of inflammation are usually strikingly elevated in active systemic JIA [12]. Erythroid aplasia has also been reported [13]. Complement levels are usually increased as part of the acute- phase response, and increased levels of complement activation products were reported [14]. Differential diagnosis of SoJIA should include infectious, post-infectious etiologies, connective tissue diseases, vasculitis, malignancies and autoinflammatory syndromes, because of nonspecific clinical and laboratory findings [10]. Amyloidosis is one of the most severe complications of SoJIA [11]. Amyloid deposition on vital organs lead to increased morbidity and mortality [10]. MAS, known as secondary hemophagocytic lymphohistiocytosis (HLH), is a serious, potentially fatal, complication that is observed in SoJIA patients. The prevalence of MAS in SoJIA is 10.0% [8], and it can occur sub-clinically in 40.0%. MAS shares clinical and laboratory features with familial/genetic and sporadic/acquired HLH.

The first-line management of SoJIA was a balancing act between achieving disease control with high-dose corticosteroids. The initial pharmacologic intervention for mild cases or while awaiting a definitive diagnosis starts with non-steroidal anti-inflammatory drugs (NSAIDs). Systemic glucocorticoids and NSAIDs have been the mainstay of treatment for years [27]. If there is no response to NSAIDs, prednisolone for three to five days can be administered [10]. If joints remain clinically active, intra-articular application of triamcinolone hexacetonide can be effective [28]. MTX the most widely used conventional DMARD. It was more effective for the chronic arthritic component of SoJIA than for the systemic symptoms [29]. Cyclosporine had a specific role in the management of concomitant MAS due to its effect on T-cells [30]. Anakinra is a biologic drug that helps to decrease inflammation. It is FDA-approved to treat rheumatoid arthritis, deficiency of interleukin-1 antagonist, and neonatal-onset multisystem inflammatory disease. It is sometimes used for SoJIA, adult-onset still's disease, and other autoinflammatory syndromes [20]. Anakinra was suggested as a main contributor to the pathogenesis of chronic inflammatory diseases, including SoJIA [7]. The pharmacokinetic study of anakinra in children, suggests that higher doses used in lower-weight children [4]. Higher dosages were used to treat patients with unsatisfactory responses to standard dose therapy. Heavier patients may require more than a single dose per day [4].

The regular measurement of disease activity level is essential to monitor the disease course over time in children with JIA and allows the assessment of the efficacy of therapeutic interventions [22, 23]. Some tools are made up by pooling several individual measures in a single instrument and have the advantage of integrating multiple aspects of the disease into one summary number on a continuous scale [24]. In 2009, the first composite disease activity score for JIA, named JADAS [25]. The treatment strategies for SoJIA are different from the other JIA

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categories [5, 6]. In most cases, treatment with a systemic glucocorticoid or biologic agent is necessary, with or without conventional synthetic DMARDS. Treatment strategies for SoJIA need to be tailored according to patient-specific manifestations, primarily according to the degree of systemic features. In patients with active systemic features, treatment with a biologic agent can be part of the initial therapy [6]. The recommended biologic agents for SoJIA in clinical guidelines include anti-TNF agents, anakinra, canakinumab, and tocilizumab. This study aims to assess the safety and efficacy of anakinra as therapy for systemic onset juvenile idiopathic arthritis.

Materials and methods

Study design and period: This is a retrospective case series, conducted by reviewing the files of patients diagnosed as SoJIA according to ILAR criteria, and followed up in the pediatric rheumatology clinic in Tripoli Children Hospital from 1/2010 to 12/2017, who were refractory to first-line treatment and used anakinra as a second line treatment.

Study setting: This study was carried out in Tripoli Children's Hospital, which is one of the teaching hospitals providing a tertiary health care service with a bed capacity of 200 beds and with a number of pediatric subspecialty clinics including: cardiology, endocrine, respiratory, neurology, gastroenterology, metabolic, neonatology, nephrology and rheumatology. The latter is the governmental clinic offering pediatric rheumatology services covering all western and southern areas of Libya.

Inclusion criteria: Diagnosis of SoJIA according to ILAR criteria and use of anakinra as treatment.

Exclusion criteria: Patient on anakinra for another disease not SoJIA.

Study tool: A preformed case sheet was used to obtain the relevant data from the medical record including the following: personal data: name, age, sex, data regarding disease activity: number of active joints (before starting anakinra, after 1, 6, and 12 months after starting), inflammatory markers (before starting anakinra, after 1, 6, and 12 months after starting), physician's global assessment, data regarding treatment (date of disease onset, date of starting anakinra, previous and concomitant therapies, dose of prednisolone (before starting anakinra, after 1, 6, and 12 months after starting), dose of anakinra, JADAS 10 and systemic manifestation score at start, after 1, 6, and 12 months after starting. Laboratory variables included white blood cell count, neutrophil count, hemoglobin, platelet count, erythrocyte sedimentation rate, c-reactive protein, fibrinogen, and ferritin. data regarding treatment complications (infections, injection site reaction, gastrointestinal complications, liver enzymes). Date of treatment stop and cause of treatment stop.

Ethical considerations and consent process: An ethical approval will be obtained from the scientific committee and the head of Tripoli Children's Hospital before starting the study.

Statistical analysis: The collected data was coded and SPSS software was used for analysis, frequency, percentage, mean, and SD were used for descriptive statistics. Inferential statistics was used accordingly, considering $p< 0.05$ as statistically significant.

Results

In this study, 12.2% of the total patients of SoJIA in the Pediatric Rheumatology Clinic in Tripoli Children's Hospital from 2010 to 2017, who fulfilled the ILAR diagnostic criteria for SoJIA. Among them, 40.6% patients received anakinra as part of their treatment regimen. The mean age at presentation of SoJIA of the patients was

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6.85±4.74 years. the youngest patient was one year old, and the oldest patient was 16 years old. furthermore, male to female ratio who received anakinra was 1: 2 ratios. With regard to prednisolone dose at zero, one month, and six months after starting anakinra, before start anakinra: High dose was in 13 cases (100%), at one month after start anakinra: Low dose was in 10 cases (77.0%) and high dose was in three cases (23.0%). At six months after start anakinra: Low dose was in 12 cases (92.0%) and high dose was in one case (8.0%).

Table 1: Prednisolone dose at zero, one month, and at six months after starting anakinra

Steroid m/Kg	before last visit	one month	three months	six months	12 months
Case-1	01.0	0.20	00.1	00.1	00.0
Case-2	0.51	0.51	00.3	00.3	00.8
Case-3	00.8	0.15	0.07	0.07	00.0
Case-4	0.94	0.40	00.2	0.06	00.0
Case-5	01.0	0.30	00.0	0.0	00.0
Case-6	0.66	0.38	0.34	0.34	00.2
Case-7	0.37	0.35	0.30	0.30	00.3
Case-8	01.0	0.52	0.15	0.10	00.2
Case-9	0.50	0.51	0.30	0.0	00.0
Case-10	0.76	0.30	0.30	0.0	00.0
Case-11	0.35	0.23	0.23	02.0	02.0
Case-12	0.31	0.30	0.30	0.10	00.0
Case-13	01.0	00.0	00.50	01.0	00.0

The total number of patients received MTX before start anakinra 13 patients (92.3 %). **Table 2** shows the age of the patients at which they received anakinra. The mean age of starting anakinra was 9.4±4.6 years and the minimum age was 2.08 years, while the maximum age was 16.92 years. Table 3 shows the duration of anakinra administered to the patients with the majority for more than one year (61.53%). Intravenous methylprednisolone pulse therapy was administered to 58.3% of the patients. The remaining patients did not receive pulse therapy (41.7%).

Table 2: Age at receiving anakinra in the children's patients

Age at receiving anakinra	Frequency	Percent
< 4 years	1	7.6 %
4 - 10 years	8	61.5 %
> 10 years	4	30.7 %
Total	**13**	**100.0%**

Table 3: Duration of anakinra treatment in Libyan children's patients

Duration of anakinra	Frequency	Percent
< 6 months	3	23.07%
6 months to one year	2	15.38%
> one year	8	61.53%
Total	**13**	**100.0**

Figure 1 shows the frequency of the children's patients for methylprednisolone pulse, with the majority of one pulse of methylprednisolone while the lowest of six methylprednisolone pulses. **Figure 2** shows concomitant drug before start anakinra. Concomitant drug before start of anakinra with MTX of 92.3% and steroids in all the patients.

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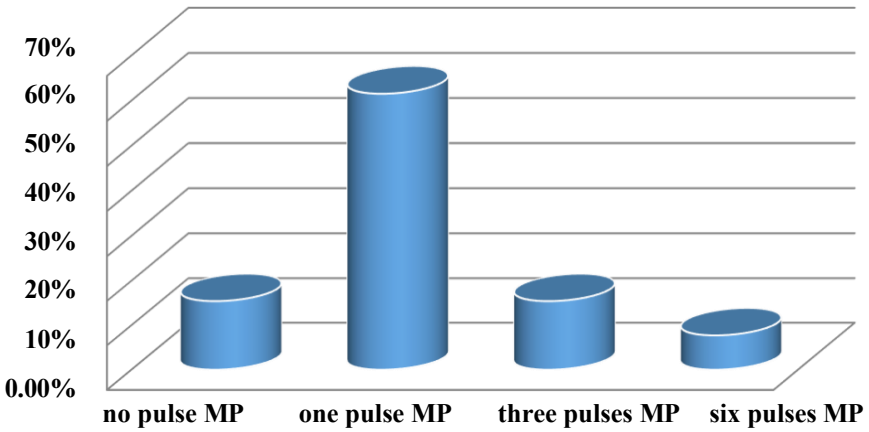

Figure 1: Methylprednisolone pulse

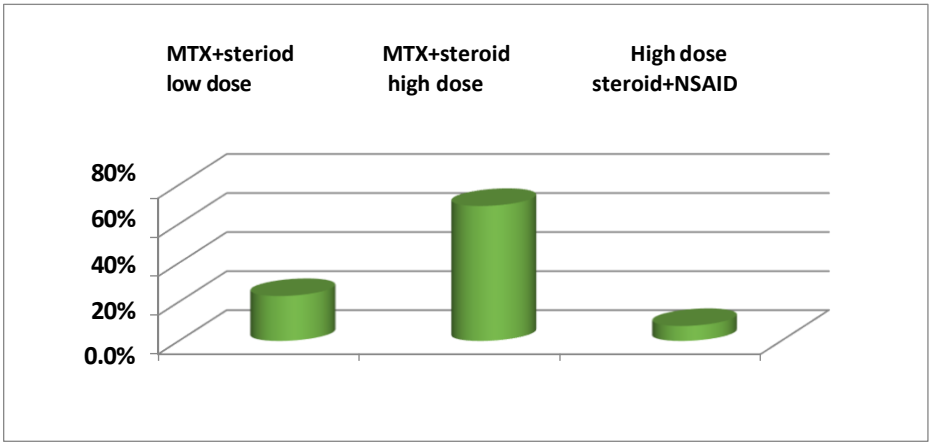

Figure 2: Concomitant drug before start anakinra

In this study, 23.0% failed biology before anakinra and 77.0% did. **Table 4** shows JADAS 10 score (before one month, three months, six months, and12 months): Juvenile arthritis disease activity score (Jadas10)

Table 4: Frequency of JADAS10 score in different intervals

Jadas10	Before	one month	three months	six months	12 months
Case -1	21.1	00.0	00.0	00.0	00.0
Case -2	21.7	08.8	00.0	10.0	12.6
Case -3	24.5	02.0	06.5	02.0	00.0
Case -4	28.0	20.0	00.0	00.0	00.0
Case -5	31.8	00.0	00.0	03.5	00.0
Case -6	20.0	12.0	13.0	12.0	00.0
Case -7	20.0	00.0	10.2	16.2	29.8
Case -8	36.0	00.0	00.0	00.0	00.0
Case -9	28.5	00.0	00.0	00.0	00.0
Case -10	10.4	00.0	00.0	00.0	00.0
Case -11	15.5	00.0	00.0	00.0	38.0
Case -12	28.5	00.5	00.3	00.4	10.9

After 12 months of treatment, 66.6% of the patients showed significant clinical improvement, reaching a score of 0, reflecting inactive disease. However, 16.6%patients had moderate disease activity, with scores ranging from 10.9 to 29.8, 16.6% patients had persistent high disease activity, with scores ranging from 12.6 to 38.

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Table 5: Commitment drug after of anakinra after one year, noticed side effects of anakinra

Side effect of anakinra	Percent
Injection Site Reaction	100%
Anaphylactic Reaction	0.0%
Headache	0.0%
Vomiting	0.0%
Arthralgia	0.0%
Nasopharyngitis	0.0%
Nausea	0.0%
Diarrhea	0.0%
Neutropenia	0.0%
High Transaminase	15.3 %
Cholesterol Elevation	7.6 %
Thrombocytopenia	0.0%
Hypernatremia	0.0%
Constipation	0.0%
Hyperkalemia	0.0%
Neutropenia	0.0%
Leukopenia	0.0%
Acute Kidney Injury	0.0%
Rash	0.0%
Anxiety	0.0%
Hypothermia	0.0%
Major/minor infection	**Percent**
Major	
MAS	15.3 %
Tuberculosis	0.0%
Pneumonia	23.0%

Table 6: Side effects of anakinra

Sepsis	0.0%
Cellulitis	0.0%
Herpes Zoster- Varicella	15.3 %
Malignancy	0.0%
Death	0.0%
Minor	
URTI	23.0%
UTI (Not Requiring Hospitalization)	07.6 %

With regard to reason for discontinuation, this study found that the reasons for discontinuation of anakinra were unavailability; 23.0%. remission: 46.1%, inefficacy: 15.3%, and side effect: 15.3%.

Regarding prognosis switch to the other biology after anakinra: two patients later switched to tocilizumab (Il-6 Inhibitor) due to inadequate response. Five patients from the total patients were switched to tocilizumab after anakinra was discontinued, mainly due to lack of availability or suboptimal response. In two patients, cyclosporine used to treat mas after stopping anakinra.

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Discussion

This retrospective study demonstrates that anakinra is an effective and relatively safe treatment for patients with refractory SoJIA in a real-world clinical setting. The current findings align with the established literature on il-1 inhibition, showing rapid disease control, significant improvement in composite disease activity scores, and a potent corticosteroid-sparing effect. The rapid reduction in jadas10 scores observed within the first month of treatment underscores the critical role of il-1β in the pathogenesis of SoJIA and confirms the swift mechanism of action of anakinra [17]. The high rate of clinical remission (66.7% at 12 months) in our cohort, which consisted of patient's refractory to first-line therapies, highlights the transformative potential of targeted biologic therapy in this severe disease. A particularly significant finding was the steroid-sparing capacity of anakinra. Over half of our patients were able to completely discontinue corticosteroids within a year. This is a crucial outcome, as mitigating the severe long-term side effects of corticosteroids such as growth suppression, osteoporosis, and cataracts is a primary goal in pediatric rheumatology. This finding compares favorably with studies by Pardoe et al. [19] and Gattorno et al. [18], who reported significant steroid dose reduction or discontinuation in responders. The safety profile in our cohort was manageable and consistent with the known effects of anakinra. The universal occurrence of injection site reactions, while a frequent cause of discomfort, did not lead to treatment discontinuation in any patient and could be managed with supportive measures. The incidence of serious infections was low, and no opportunistic infections were noted. However, the occurrence of mas in two patients is a sobering reminder that SoJIA itself carries a risk of this life-threatening complication. While anakinra is itself a recognized treatment for MAS, its emergence in some patients on therapy indicates the complex and volatile nature of SoJIA and necessitates vigilant monitoring. This study has several limitations inherent to its retrospective design, including a small sample size and the lack of a control group. The relatively short follow-up period limits our ability to comment on long-term efficacy and safety. Furthermore, a significant challenge highlighted by our results was drug unavailability, which was a reason for discontinuation in 23.0% of cases, reflecting resource limitations that can affect patient care in real-world settings. Larger-scale studies with longer follow-up are warranted to confirm these findings and identify predictive factors for response. Research should also focus on optimizing treatment strategies, including the ideal timing for initiation of il-1 inhibition and the management of patients with suboptimal response.

Conclusion: This study adds to the growing body of evidence supporting the use of anakinra in SoJIA. It confirms its efficacy in achieving rapid disease control and remission, its excellent steroid-sparing effect, and its acceptable safety profile. Despite the challenges of drug access, anakinra should be considered a cornerstone in the management of children with refractory systemic juvenile idiopathic arthritis.

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