

Case Series

Treatment of Systemic Onset Juvenile Idiopathic Arthritis with Anakinra

Irigoyen, Patricia¹; Olson, Judyann², Hom, Christine³; Ilowite, Norman¹

Schneider Children's Hospital¹, Medical College of Wisconsin², New York Medical College³

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Abstract

Objective: To describe the result of the use of anakinra in 14 patients with systemic onset juvenile idiopathic arthritis (SOJIA) patients

Methods: We performed a multi-center retrospective chart review of SOJIA patients who received anakinra. We asked members of the pediatric rheumatology list-serve to provide information regarding their experience with the use of anakinra. Five centers, including our own, provided data. All SOJIA patients in whom anakinra was used were included in the analysis. N=14

Results: Duration of therapy ranged from 3 to 28 months (mean=12 months; median = 9 months). In most patients who responded, improvement was rapid (less than two weeks) and sustained. Fever resolved in three patients who were febrile at initiation of therapy. Concomitant medications included methotrexate (n=6), prednisone (n=6), NSAIDs (n=6), and cyclosporine (n=1). Previous failed therapy included prednisone (n=7), NSAIDs (n=7), methotrexate (n=6), etanercept (n=4), infliximab (n=1), and cyclosporine (n=1). Anakinra therapy resulted in complete resolution of extra-articular symptoms in all patients. In addition, all patients had normalization of laboratory values. Fourteen of fourteen patients had improvement in their arthritis; 10/14 had complete resolution of arthritis. No serious infections were reported.

Conclusion: All patients in this study had a good response and did not have serious side effects. Most striking was the improvement of joint symptoms in all patients in a population that was refractory to previous therapy. The study likely has a selection bias as centers that had success with anakinra may have been more likely to submit data. Blinded prospective studies on the treatment of systemic onset JRA with anakinra should be performed.

Introduction

Systemic onset juvenile idiopathic arthritis (SOJIA) is perhaps the most identifiable, and potentially most severe, phenotype of the various arthritis subtypes. Accounting for 10-20 % of children with JIA, the systemic subtype can exhibit a prolonged course of systemic features with polyarticular joint involvement.

[1]

Children with SOJIA receive traditional treatment with corticosteroids, NSAIDs, methotrexate, and other immunosuppressive medications. Despite these therapies, about 30% of children will develop destructive polyarthritis with long term morbidity and disability. More recently, TNF α inhibitors have been used with moderate success to treat patients with SOJIA and persistent polyarthritis.[2] However, a significant number of children have persistent polyarticular disease as well as laboratory evidence of chronic inflammation in spite of aggressive anti-inflammatory or immunosuppressive therapy. [2] Anakinra is identical to a naturally occurring nonglycosylated human form of IL-1 Receptor antagonist (IL-1Ra) with the exception of 1 N-terminal methionine. [3] IL-1Ra is partly responsible for the regulation of IL-1 α and IL-1 β by competitively binding with high avidity to the type 1 IL-1 receptor (IL-1R). Anakinra is administered subcutaneously, at doses of 1mg/kg up to 100mg daily.

Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1 receptor, preventing docking of the accessory protein and subsequent intracellular signaling events. Anakinra consequently has a number of anti-inflammatory effects, including suppression of proinflammatory cytokine production including TNF and IL-6, decreased production of collagenases by chondrocytes, decreased production of adhesion molecules by endothelial cells, fibroblasts, and osteoclast precursors. Anakinra has been shown to be safe and modestly effective in adult rheumatoid arthritis.[4] Preliminary data suggests efficacy in polyarticular course JIA. [5] Case reports have suggested particular efficacy of anakinra in refractory cases of SOJIA. [6] Our paper describes a retrospective chart review analyzing the experience of anakinra in systemic onset JRA patients who had failed previous therapies, including TNF-alpha inhibition.

Patients and Methods

Institutional review board approval was obtained for this retrospective chart review at each participating center. The pediatric rheumatology list-serve, reaching 526 rheumatologists worldwide, established by Dr. Peter Dent (McMaster University) , was used as a tool to identify refractory SOJIA patients who had been treated with anakinra. Five centers agreed to participate, providing data on fourteen patients. All systemic onset JIA patients who had received anakinra at these centers were included in the analysis. The diagnosis of SOJIA was determined by each center, as were criteria for lack of response. We chose the following significant indicators of response to therapy in SOJIA: rise in hemoglobin and albumin, decrease in platelet count, Westergren erythrocyte sedimentation rate (ESR), prednisone dose and number of active joints. An active joint was defined as having non-bony swelling or, if no swelling was present, limited range of motion combined with either tenderness or pain on movement. These data were obtained at the visit preceding initiation of anakinra therapy, throughout the course of therapy, and at the last available patient visit while on treatment. In addition, the centers provided information regarding previous failed therapy, concomitant therapy, age of disease onset, extra-articular manifestations, and any adverse events. All data were collected via retrospective chart review at each participating institution.

Ten of 14 patients had extra-articular manifestations at the time of initiation of anakinra. These included rash (n=9), fever (n=3), myalgia (n=1), hepatomegaly (n=2), and lymphadenopathy (n=1). All of

the patients had active arthritis, with joint counts ranging from 1 to 49 active joints (mean= 14, median=10). Duration of therapy ranged from 3 to 28 months (mean=12 months; median = 9 months). Concomitant medications included methotrexate (n=6), prednisone (n=6), NSAIDs (n=6), and cyclosporine (n=1). Previous failed therapy included prednisone (n=7), NSAIDs (n=7), methotrexate (n=6), etanercept (n=4), infliximab (n=1), cyclophosphamide (n=1), and cyclosporine (n=1). Age of onset for these patients ranged from 1 to 15 years, with a mean of 7 years old at onset.

Results

Fourteen of 14 patients had improvement in their arthritis and 10/14 had complete resolution of arthritis (Figure 1).

Anakinra Effect on Arthritis

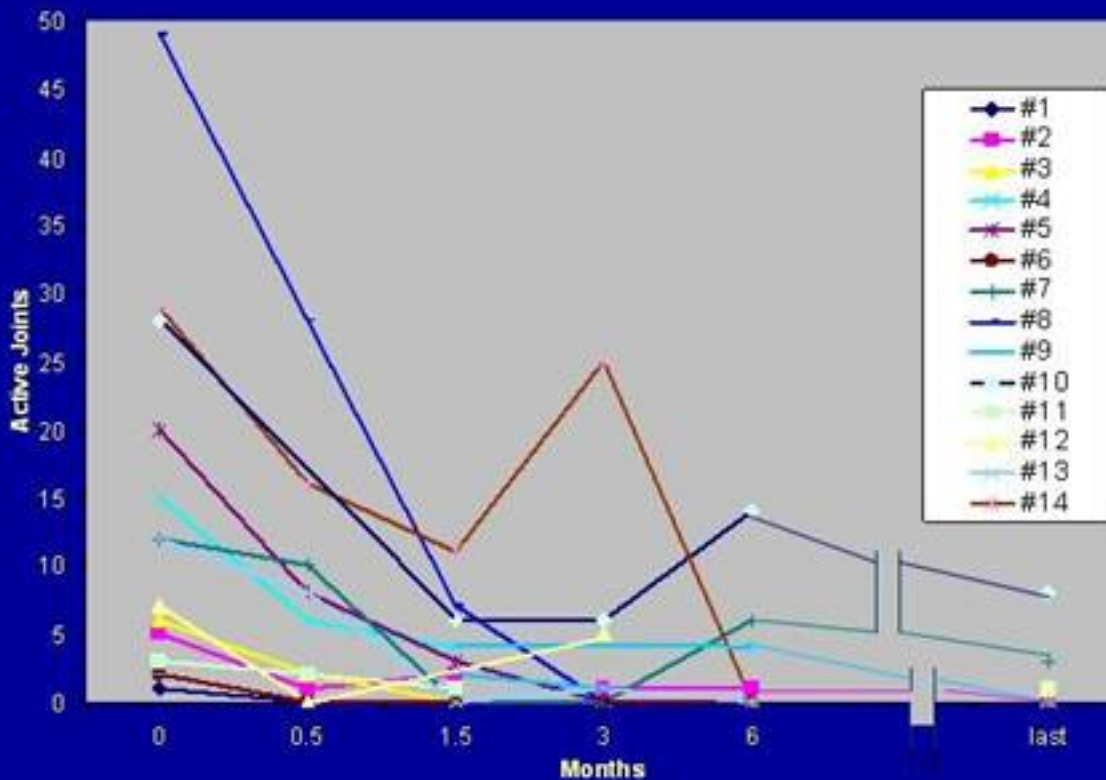


Figure 1. Average active joint count following anakinra therapy.

Anakinra therapy resulted in complete resolution of extra-articular symptoms within 3 months in all patients with active systemic features (Figure 2).

Extra-Articular Manifestations

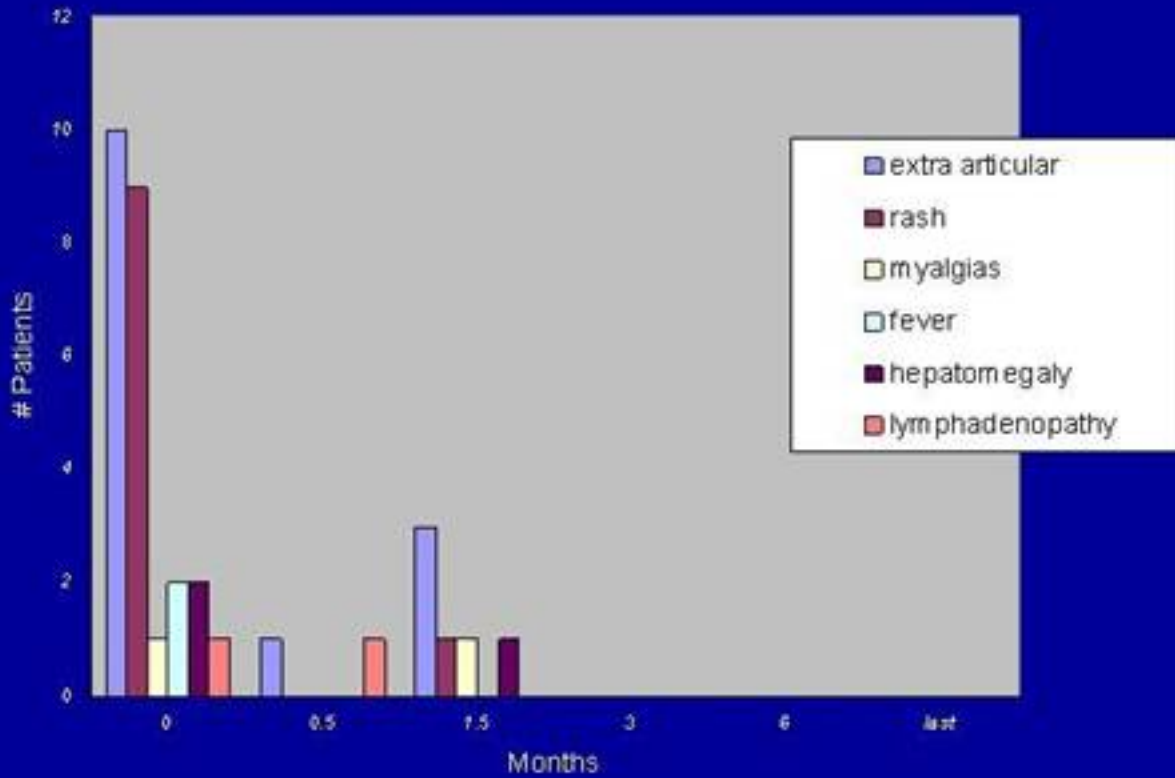


Figure 2. Resolution of extraarticular features

In addition, normalization of laboratory values was seen in all patients (Figures 3-5).

Anakinra Effect on CBC

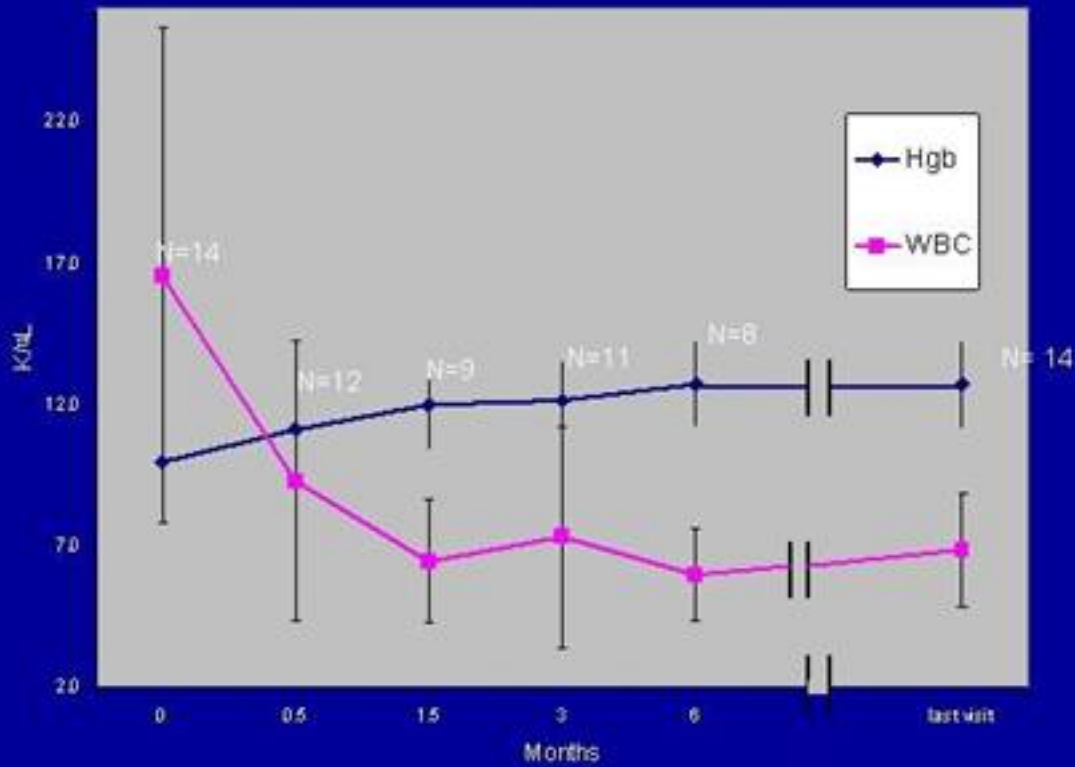


Figure 3. Average hemoglobin level and white cell count after anakinra therapy

In most patients who responded the improvement was immediate (less than two weeks) and sustained.

Anakinra Effect on ESR

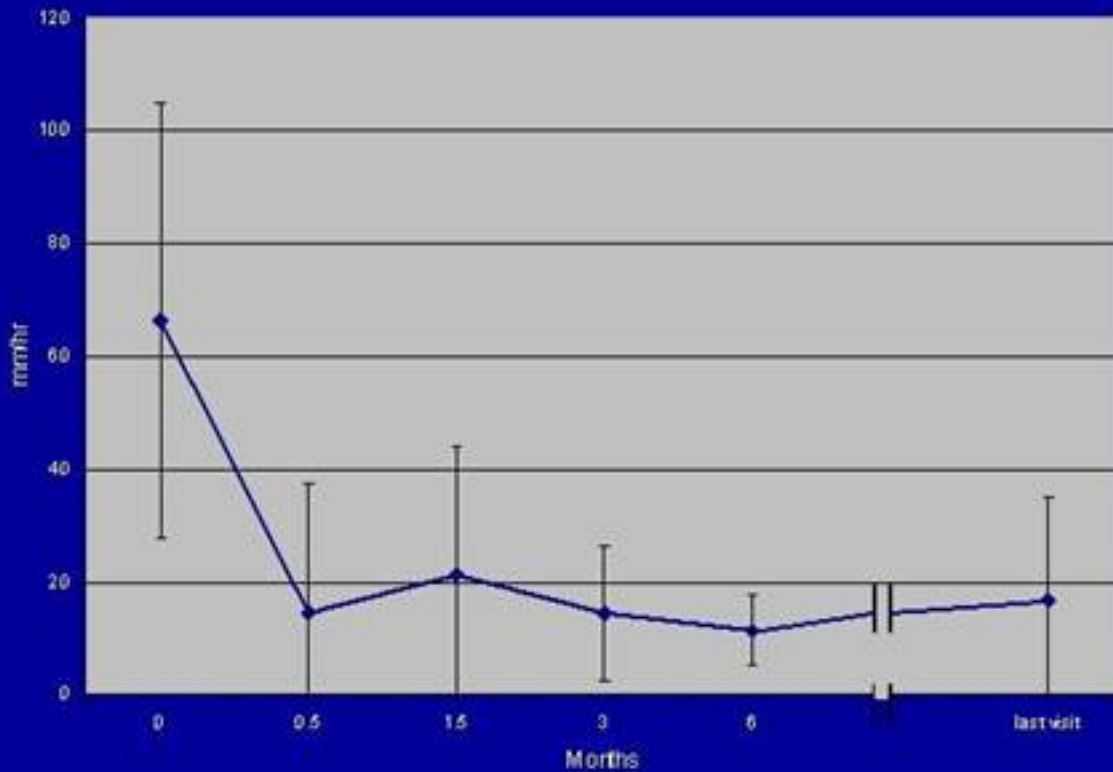


Figure 4 Average erythrocyte sedimentation rate (ESR) following anakinra therapy.

Fever resolved in the three patients who were febrile at initiation of therapy. However, injection site reactions were frequently seen. One patient chose to discontinue anakinra due to injection site pain. No serious infections were reported.

Anakinra Effect on Platelets

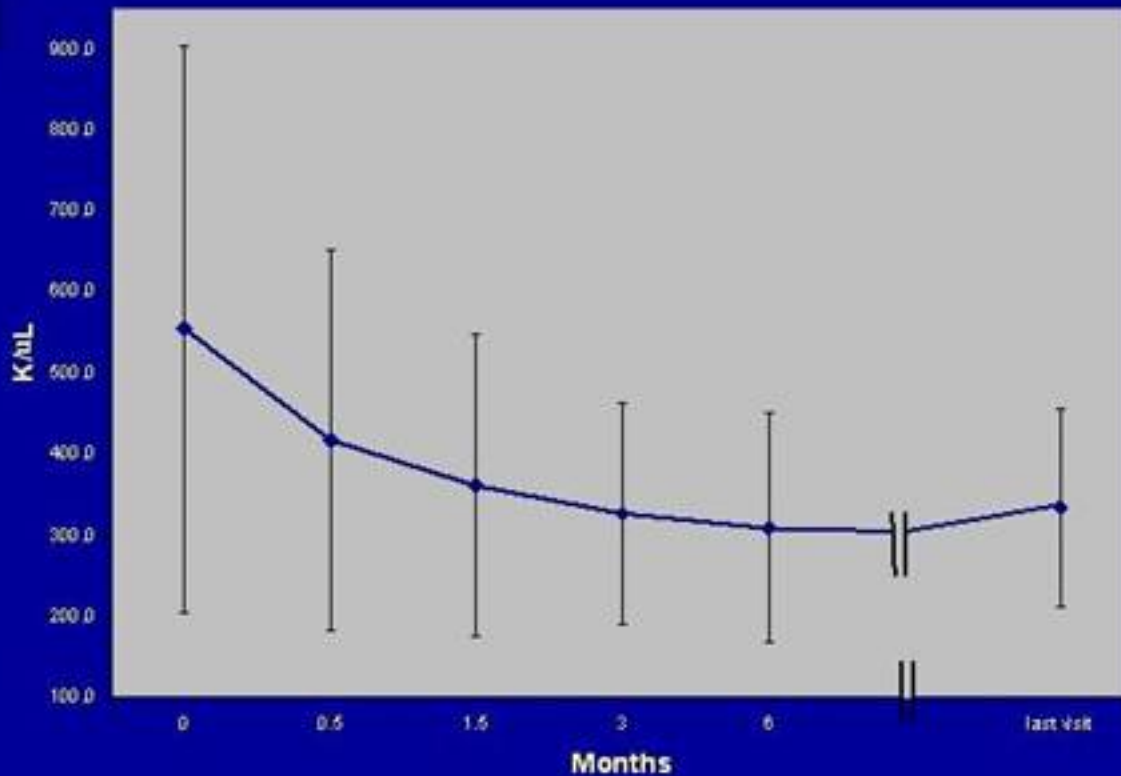


Figure 5 Average number of platelets following anakinra therapy.

Discussion

Between 8,000-30,000 children in the US have SOJIA, making SOJIA a rare disease and posing significant challenges in designing clinical research studies. SOJIA usually presents with systemic features at onset with or without arthritis. These systemic features include high spiking fever, characteristic rash, hepatosplenomegaly, polyserositis, pericarditis, lymphadenopathy, anemia, leukocytosis, and thrombocytosis. More than 80% of patients have polyphasic or chronic persistent disease course [7] and more than half suffer poor outcome. [8-10]

Predictors of poor outcome (joint damage, poor functional status) include young age at diagnosis, disease duration of greater than 5 years, persistent systemic symptoms (defined by prolonged fever or sustained treatment with corticosteroids) or the presence of thrombocytosis, high sedimentation rate, and multiple active joints after 3-6 months of disease. [11-12] Although there is an ever-expanding body of evidence about the safety and efficacy of various agents in polyarticular JRA, only select systemic onset patients (those with a polyarticular course but without significant systemic features) are included in these studies, therefore the results may not be easily generalized to all SOJIA patients. The current standard of care is to

use methotrexate and etanercept as second and third line agents in this disease; it can be argued that efficacy has not been proven for either of these therapies. [13]

The data on effectiveness of methotrexate in SOJIA are somewhat contradictory. A collaborative study between the USSR and USA regarding the effectiveness of methotrexate in JRA found no difference in response rates among the different subtypes with an overall response rate of 60-89%, however the number of systemic patients receiving the dose that was found to be effective, was only 9 (20%). [14] Woo et al did not find methotrexate to be effective treatment using the JRA core criteria in systemic patients. [15] In comparison, Ruperto et al in their open label uncontrolled study of over 600 patients with JRA treated with 10mg/m²/week of methotrexate, found that the systemic subset had a response rate to standard dose methotrexate of 80%. [16] In another uncontrolled study, al-Sewairy and colleagues found 89% of SOJIA patients had significant improvement in their joint count, functional class and systemic features. [17]

There is also a growing amount of evidence that SOJIA patients' response to etanercept is less predictable when compared to other polyarticular JRA patients. In several studies, when the systemic onset polyarticular course subgroup is examined separately, more SOJIA patients on etanercept had a disease flare and/or poor response in comparison to the other JRA subgroups. [18-21] The German etanercept registry included 66 patients with SOJIA who were evaluated according to the JRA core set criteria. At 12 months only 24% SOJIA patients had a 70% response rate compared to 54% of the other subtypes and 14 (21%) patients had discontinued treatment owing to lack of efficacy. [22]

The initial study of etanercept in polyarticular course JIA [18] 22 SOJIA patients (without significant systemic features), 17 (77%) qualified as responders in the open label phase of the randomized withdrawal trial. During the blinded phase 7/8 SOJIA patients flared in the placebo group and 4/9 (44%) flared in the etanercept group. In contrast, only 18% of children with other subtypes of JIA flared in the placebo group. In the long-term open label follow-up study [19], 25% of subjects had SOJIA; only 47% achieved 70% improvement as compared to 62% with other disease onset subtypes. Less than 50% of subjects with SOJIA were found to have satisfactory response to etanercept.

Previous reports highlight the difficulty of treating SOJIA patients who are refractory to these standard therapies. Several case series show some response with several different agents. Drugs which have been tried, with varying levels of success, have been IVIG, cyclosporine, thalidomide, statins, cyclophosphamide, and stem cell transplant.[23-28] In light of these studies and reports, the prompt and sustained response to anakinra and lack of serious adverse events of our refractory patients is very encouraging.

The different response rates of JIA subtypes can most likely be attributed to underlying differences in pathophysiology, which is evidenced by differences in their cytokine profiles. There have been several studies to evaluate the production of cytokines and cytokine inhibitors in blood samples from patients with SOJIA, which have on the whole supported the concept that inflammatory cytokines include variably IL-1, IL-6, and IL-2 as well as other molecules associated with inflammatory cytokines (IL-1Ra, sTNFR). [29-37] Gene expression studies have also suggested increased IL-1 in SOJIA Expression profiling using microarray technology suggests the presence of inflammatory cytokine signatures unique to active SOJIA.

[38] This is consistent with the growing evidence that children with SOJIA do not respond to etanercept as well as other polyarticular JIA patients. Our data, as well as recent case series, suggest SOJIA is an example of this diversity with generally only moderate response to TNF inhibitors, but marked rapid improvement in response to IL-1 inhibition.

In this retrospective chart review we found that anakinra appeared to be safe and effective in the treatment of SOJIA. Most striking was the improvement of joint symptoms in all patients in a population that was refractory to previous therapy, including TNF alpha inhibition. In addition, anakinra appeared to be effective in treatment of extra articular manifestations of SOJIA. The small sample size, retrospective nature, and methods of patient collection limit our ability to interpret these results to the general population of SOJIA patients. Our study likely has a selection bias as centers that had success with anakinra were more likely to participate in the review. In addition, while our data show improvement of disease, no validated set of criteria has been determined to evaluate the response of systemic features of SOJIA. Outcome measures for SOJIA need to be validated in order to enable blinded prospective studies on the treatment of systemic onset JIA with anakinra and other promising biologic therapies.

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