Case Report

# Effective Use of the Recombinant Interleukin 1 Receptor Antagonist Anakinra in Therapy Resistant Systemic Onset Juvenile Rheumatoid Arthritis

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***ABSTRACT.*** Systemic onset juvenile rheumatoid arthritis (SOJRA) is a multisystem disease characterized by high fever, rash, arthritis, serositis, splenomegaly, and laboratory evidence of systemic inflammation. Anticytokine therapies show promise in the treatment of chronic arthritides in children. We describe the use of the recombinant interleukin 1 receptor antagonist anakinra in 2 patients with therapy resistant SOJRA. Both patients experienced immediate and sustained resolution of symptoms and laboratory markers of inflammation, in one case after years of treatment with other immunosuppressive therapies. (J Rheumatol 2004;31:2071–5)

*Key Indexing Terms:*
JUVENILE ONSET STILL DISEASE
HEMOPHAGOCYTIC SYNDROME
ANAKINRA
INFLIXIMAB
JUVENILE RHEUMATOID ARTHRITIS

Systemic onset juvenile rheumatoid arthritis (SOJRA) is a multisystem disease characterized by high fever, rash, arthritis, serositis, splenomegaly, and laboratory evidence of systemic inflammation. Conventional treatment consists of corticosteroids and other immunosuppressive medications. Anticytokine therapies have been developed that show promise in the treatment of chronic arthritides in children. We describe the use of the recombinant interleukin 1 (IL-1) receptor antagonist anakinra in 2 patients with therapy resistant SOJRA. Both patients experienced immediate and sustained resolution of symptoms and laboratory markers of inflammation, in one case after years of treatment with other immunosuppressive therapies. This is the first report describing effective treatment of SOJRA with anakinra.

## CASE REPORTS

*Patient 1*. A 12-year-old Caucasian boy presented with a one-week history of fevers, sore throat, cervical lymphadenopathy, evanescent macular rash, joint pains, myalgia, fatigue, cough, and chest pain. On admission he was febrile to 38.9°C. His examination was significant for a pericardial friction rub and warmth of both ankles. His knees had effusions and were painful on movement. A macular, nonpruritic, salmon colored rash with central pallor was visible on his trunk and extremities. Laboratory evaluation showed a white blood cell (WBC) count of 22,000, hemoglobin 13.4 g/dl, platelet count 247, erythrocyte sedimentation rate (ESR) 48 mm/h, and C-reactive protein (CRP) 36 mg/dl. Investigation for infection included: nasopharyngeal swab negative for respiratory syncitial virus, adenovirus, and parainfluenza virus; polymerase chain reaction (PCR) negative for *Mycoplasma pneumoniae*; negative stool, blood, and urine cultures; negative blood mycology cultures; PCR analysis of blood negative for Epstein-Barr virus, cytomegalovirus, herpes simplex virus, parvovirus, and *Ehrlichia*; negative serologies for *Bartonella henselae*, parvovirus, *Mycoplasma*, hepatitis A, B and C viruses, and *Histoplasma capsulatum*. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) were negative. Initial chest radiograph was normal, but within 2 hospital days he developed left and right lower lobe infiltrates and a small pleural effusion. Ibuprofen, ceftriaxone, and azithromycin were started, with no improvement in symptoms. He continued to experience daily evening fevers up to 38.9°C, with complete defervescence the next day. His rash intensified during febrile episodes, but would resolve upon defervescence. The diagnosis of systemic JRA was considered. Intravenous methylprednisolone (2 mg/kg/day divided every 6 h) was begun on hospital day 4 because of persistent severe joint pain and swelling, myalgias, and significant malaise. His symptoms improved, but worsened when his steroid dose was decreased. On hospital day 10, pulse intravenous methylprednisolone (1 g) was started daily for 3 days, with improvement in joint pain and swelling. Because of the severity of his symptoms, the exclusion of other diseases, and the continued consideration of Still's disease, infliximab (5 mg/kg/dose) was given on days 12 and 14. His fevers resolved, his joint symptoms continued to improve, and he was discharged home on the 14th day of illness taking 40 mg per day prednisone and 15 mg weekly methotrexate (MTX).

At home he experienced nightly fevers to 104°F, rash, arthritis, shoulder pain, back pain, and cough. A chest radiograph showed improved but persistent infiltrates, cardiomegaly, and pleural effusions. A chest and abdominal computerized tomography (CT) scan showed splenomegaly, moderate cardiomegaly, a moderate pericardial effusion, and pleural effusions. His prednisone dose was increased to 60 mg daily. On the 21st day of illness, he developed a new petechial rash. Evaluation showed a WBC count of $4 \times 10^3$/ml, hemoglobin 9.7 g/dl, and platelet count $4 \times 10^3$/ml. His ESR was 61 mm/h, CRP 19 mg/dl, lactate dehydrogenase was 1292,

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fibrinogen was elevated at 496, prothrombin time was elevated at 15.6, and ferritin was 26,846 ng/dl. Triglycerides and transaminases were normal. The MTX was discontinued. Infliximab was given again (10 mg/kg total) on the 25th and 32nd day of illness. A bone marrow biopsy showed no evidence of malignancy, but histiocytic cells were seen containing platelets, erythrocytes, and myeloid elements. The macrophage activation syndrome (MAS) was diagnosed, and a standard treatment protocol consisting of VP-16, cyclosporin A (CSA), and dexamethasone was begun. In addition, he continued to receive infliximab infusions (5 mg/kg/dose) weekly for 5 weeks for persistent arthritis. Six weeks after initiation of dexamethasone, CSA, VP-16, and infliximab infusions his platelet count and WBC improved, but high daily fevers, rash, myalgias, and swelling and warmth of his wrists, knees and ankles persisted. The diagnosis of SOJRA was confirmed based on daily fevers accompanied by a characteristic rash and polyarticular arthritis of greater than 6 weeks' duration. Anakinra (100 mg subcutaneously daily, 67th day of illness) was begun for persistent symptoms. Within 24 h he reported resolution of his fevers, rash, myalgia, and joint pains. No rash, joint warmth or swelling, or fevers were noted on examination one week after starting anakinra. Four weeks later his hemoglobin and ferritin levels had improved, and his CRP had normalized for the first time since the start of his illness. Eighty-five days after starting anakinra, his hemoglobin, ESR, ferritin, WBC count, and platelet count had normalized. His medications were slowly tapered, and 6 months after starting anakinra he was symptom-free, using no other medications. Figure 1 summarizes the treatment course and laboratory evaluations.

*Patient 2*. A previously healthy 4-year-old Caucasian boy presented with fever, diarrhea, abdominal pain, rash, and neck pain 2 weeks after receiving a hepatitis B vaccination. Initial laboratory evaluation showed a WBC of 41 $\times 10^3$/ml, CRP 15 mg/dl, hemoglobin 11, platelet count 206 $\times 10^3$/ml. Chest CT showed pleural effusions and basilar infiltrates. He was treated with broad spectrum antibiotics as well as intravenous immunoglobulin for concerns of Kawasaki's disease, but his condition worsened, requiring admission to the intensive care unit and intubation for respiratory failure. Tests for infectious etiologies, including streptococcus, Epstein-Barr virus, cytomegalovirus, hepatitis A, B and C, parvovirus, *Rickettsia*, *Mycoplasma*, *Ehrlichia*, *Legionella*, *Chlamydia*, respiratory syncytial virus, influenza viruses, typhus, Q fever, and bacterial and fungal cultures indicated no recent infection. His ANA, extractable nuclear antigen, rheumatoid factor, lupus anticoagulant, anticardiolipin antibodies, and ANCA were all negative. Skin biopsy showed findings consistent with urticaria. He was treated with methylprednisolone (2 mg/kg/day), with improvement and extubation after 11 days. During his hospital stay he continued to have fevers, rash, and abdominal pain. His WBC reached a peak of 130 $\times 10^3$/ml. Bone marrow biopsy showed a predominance of myeloid cells, but no blasts or other indication of malignancy. He was discharged home on a slow steroid taper.

He continued to have abdominal pain, fevers, rash, irritability, respiratory distress, and weakness requiring intravenous as well as oral steroids. Three months later (around the 150th day of illness) he was noted to have decreased range of motion of his ankles. Given his fevers, rash, elevated ESR, and arthritis, he was diagnosed with SOJRA. MTX was started (15 mg/m$^2$) on the 156th day of illness. For the next 2 months he had fewer fevers, but continued to experience pain with movement of his hands, ankles, feet, and wrists, as well as a worsening cough. Chest radiograph continued to show infiltrates, and a chest CT showed fine reticular infiltrates throughout. MTX was discontinued. An open lung biopsy was performed, showing interstitial fibrosis with acute inflammation consistent with rheumatologic lung disease versus infection. Investigation for infection was normal. It was felt that his lung disease was a consequence of SOJRA.

Cyclophosphamide was started (240th day of illness), and he received 13 monthly doses (500–1000 mg/m$^2$). He continued oral steroids at the lowest tolerable dose. During this period, his course was complicated by a herpes zoster infection, several cases of pneumonia, recurrent sinusitis, and a T5 compression fracture requiring spinal fusion. After 13 doses of cyclophosphamide he was clinically improved and cyclophosphamide was stopped, but he continued to have laboratory markers of inflammation. Over the next year he continued to experience flares of illness requiring oral as well as intraarticular steroid treatments, and etanercept was begun on the 1052nd day of illness (12.5 mg subcutaneously twice weekly). His fevers, morning stiffness, and rash resolved. Laboratory evaluation showed improvement in his systemic inflammation, and he was able to discontinue his steroids (1167th day of illness). One year later he experienced a severe flare in his illness, with rash, fevers, arthritis, and elevated WBC count and ESR. Prednisone was restarted but it was not possible to taper it. Infliximab was started (3 mg/kg/dose) and etanercept discontinued. Cyclophosphamide was restarted (1 g/m$^2$) and he received 15 pulses, with only marginal improvement in symptoms. Despite these interventions, fevers, fatigue, and joint pain and stiffness persisted. Anakinra was started on the 1925th day of illness. Within 2 days, he reported resolution of rash, fevers, pain, fatigue, and joint stiffness. His active joint count decreased from 22 to zero 3 weeks after starting anakinra. Corticosteroids were tapered over the next 3 months. His WBC, platelet count, and hemoglobin have all normalized. His ESR dropped precipitously after initiation of anakinra and has remained normal except for one measurement. He has remained symptom-free, taking no medications except for anakinra, for over one year. Figure 2 summarizes his treatment course.

## DISCUSSION

This is the first published report describing the use of a recombinant IL-1 receptor antagonist in SOJRA. Although the severity of illness in the first patient required aggressive treatment before a diagnosis could be firmly established, the symptoms of characteristic rash, daily fevers, and polyarticular arthritis persisting longer than 6 weeks confirmed the diagnosis of SOJRA. Both patients had severe disease that was ultimately refractory to numerous immunosuppressive therapies including corticosteroids, MTX, and the anti-tumor necrosis factor-α (TNF-α) agents infliximab and etanercept. In addition, cyclosporine and VP-16 were used for the treatment of MAS in the first patient. Although these therapies were beneficial in temporarily alleviating symptoms, both patients continued to experience active disease. Anakinra was given to both because of the severity of their disease and resistance to conventional treatment, and both reported immediate responses, with resolution of fevers, rash, and arthritis. Laboratory analysis showed rapid normalization of blood cell counts and markers of inflammation. Their symptoms have not returned, and all other medications have been discontinued. Our second patient has remained symptom-free for over a year, treated only with anakinra. This was after 6 years of active illness with significant morbidity related to his illness and his treatment.

Several reports have described benefit of the anti-TNF-α agents etanercept and infliximab in systemic onset RA in both adults and children, although each report showed a significant number of nonresponders. Five of 12 adult patients with Still's disease showed no response after 6 months of treatment with etanercept[1]. Concurrent medications in this report included prednisone, MTX, and nonsteroidal antiinflammatory medications. One of 3 patients with SOJRA treated with infliximab by Billiau, *et al* was ultimately refractory to therapy[2]. Elliott, *et al* report rapid,

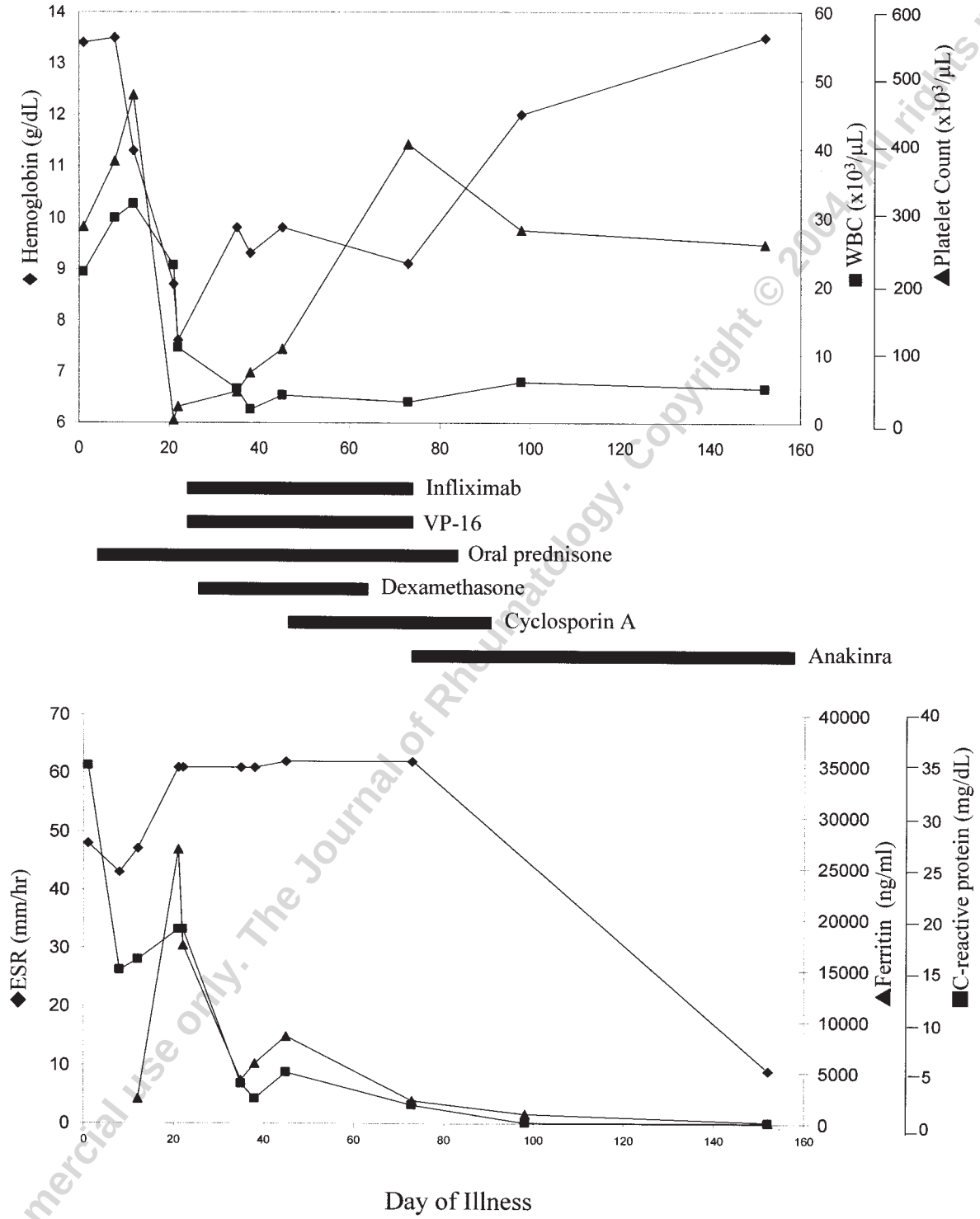


*Figure 1.* Treatment regimen and laboratory studies of Patient 1. Top panel shows hemoglobin, WBC, and platelet count during first 160 days of treatment. Bottom shows ESR, ferritin, and CRP during the same period. Treatments are as shown, duration of treatment indicated by black bars.

although transient, resolution of fever and elevated serum cytokine and CRP levels. Joint pain and tenderness were not affected, and the fever and elevated CRP returned within 2 weeks[3]. Ten Cate, *et al* treated 4 patients with therapy resistant SOJRA with etanercept for 3 to 6 months. One patient showed a dramatic response in signs of inflammation and

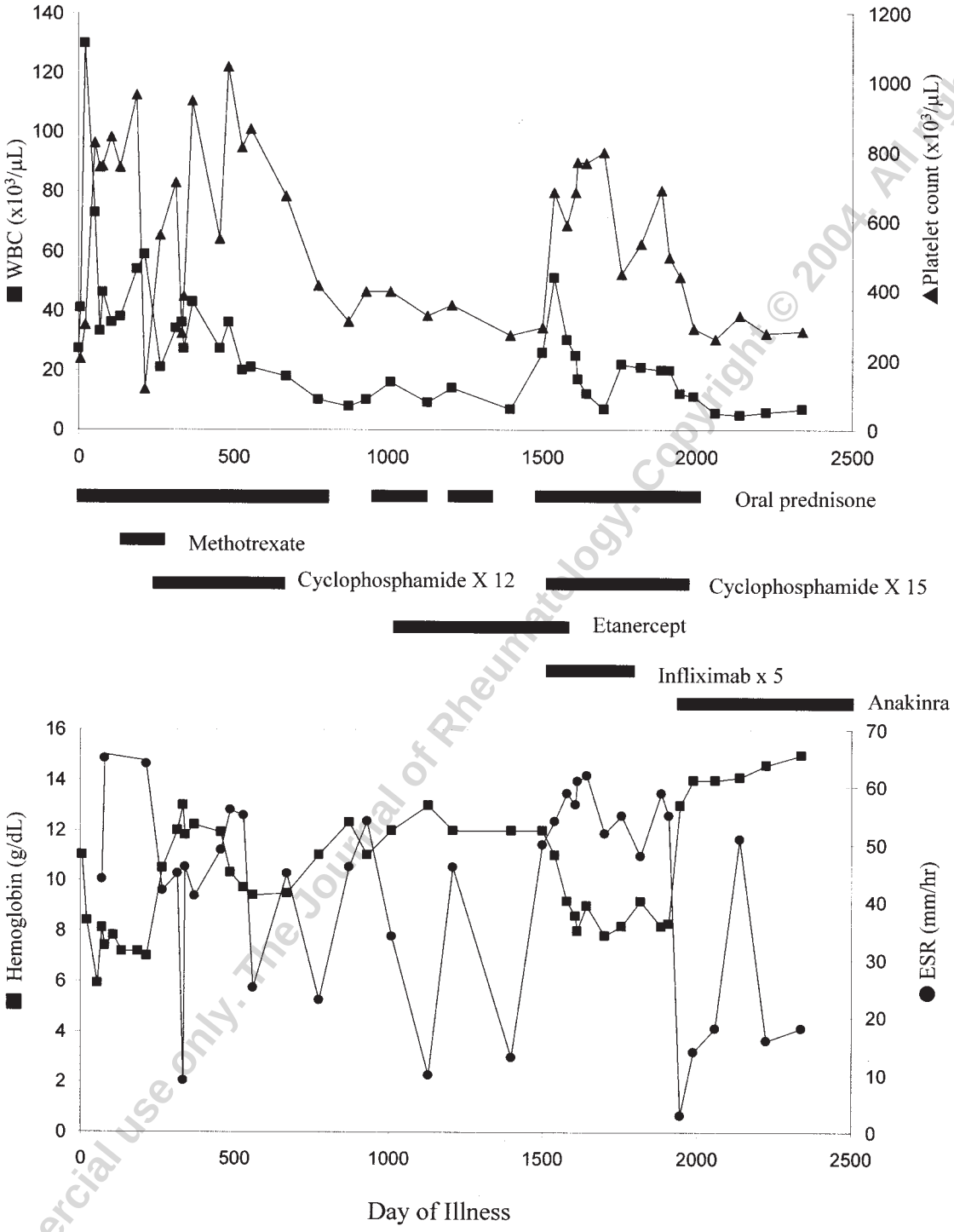


*Figure 2*. Treatment regimen and laboratory studies of Patient 2. Top panel shows WBC and platelet counts during 6 years of treatment. Bottom shows ESR and hemoglobin levels during the same period. Treatments are as shown, duration of treatment indicated by black bars.

ESR, one showed no response, and the other 2 patients had variable responses[4]. Similarly, our patients were ultimately refractory to anti-TNF-α therapies after transient responses. Both patients, however, responded immediately to anakinra with resolution of fevers, rash, and arthritis, and resolution of laboratory markers of inflammation. In addition, their responses have persisted for 6 and 15 months with no other medications.

Numerous cytokines have been implicated in the disease process of SOJRA, including IL-1, TNF-α, IL-6, IL-18, and

macrophage migration inhibitory factor, although studies have been contradictory. Yilmaz, *et al* showed significant elevation of serum IL-1ß levels in active SOJRA compared to patients with inactive disease and healthy controls[5]. Serum IL-6 levels were similarly elevated in patients with active disease compared with inactive disease and healthy controls. TNF-α levels were not different between active disease, inactive disease, and controls. Mangge, *et al* observed persistently elevated TNF-α levels in all 6 patients with SOJRA over a 36 month period, but only 2 of the 6 patients had elevated IL-1ß levels[6]. The same group reported elevated levels of serum IL-6 and IL-1ß in patients with SOJRA early in the illness[7]. Two groups found no detectable increase in serum IL-1ß levels in SOJRA[8,9]. Although these reports have led some investigators to conclude that IL-1 is not involved in the pathogenesis of SOJRA[10], IL-1 is well suited to contribute to inflammation and joint destruction in SOJRA through its numerous inflammatory and immunostimulatory effects[11]. Clinical evidence for the role of IL-1 in arthritis is supported by the effectiveness of IL-1 receptor antagonist (IL-1Ra) in adults with RA[12,13]. In addition, animal models have shown a critical role of the IL-1Ra in preventing organ damage. IL-1Ra knockout mice develop a spontaneous inflammatory arthropathy as well as fatal arterial inflammation[14,15].

Our data suggest that IL-1 is not redundant in propagating the inflammatory response in our patients with severe SOJRA. Both patients have been able to discontinue all other medications since starting anakinra, which they were unable to do taking anti-TNF-α medications, and neither patient has experienced resistance to anakinra. The responses to anakinra were so dramatic that both boys were reluctant to reduce the dose of this injectable medication, even after months without symptoms. In addition, laboratory markers of inflammation were affected by IL-1 antagonism in a rapid and sustained fashion. A striking example was the response of the anemia seen in both patients. Hemoglobin concentrations were persistently low in both patients during the entire course of their illnesses, even during TNF-α antagonism. Only after anakinra was started did hemoglobin levels return to normal.

The prominent response of these 2 patients to the IL-1Ra anakinra represents a potentially important therapeutic option for pediatric rheumatologists. Refractory SOJRA is a life-threatening disease that is difficult to treat and whose response to anti-TNF-α therapy has not been as favorable as other forms of juvenile arthritis. The effects of anakinra in our 2 patients were rapid and sustained with minimal side effects. We believe the response to anakinra in these 2 patients warrants further investigation of its use in SOJRA.

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