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Anakinra as First-Line Disease-Modifying Therapy in Systemic Juvenile Idiopathic Arthritis

Report of Forty-Six Patients From an International Multicenter Series

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Objective. **To examine the safety and efficacy of the interleukin-1 (IL-1) receptor antagonist anakinra as first-line therapy for systemic juvenile idiopathic arthritis (JIA).**

Methods. **Patients with systemic JIA receiving anakinra as part of initial disease-modifying antirheumatic drug (DMARD) therapy were identified from 11 centers in 4 countries. Medical records were abstracted using a standardized instrument, and resulting data were analyzed to characterize concomitant therapies, clinical course, adverse events, and predictors of outcome.**

Results. **Among 46 patients meeting inclusion criteria, anakinra monotherapy was used in 10 patients (22%), while 67% received corticosteroids and 33% received additional DMARDs. Outcomes were evaluated at a median followup interval of 14.5 months. Fever and rash resolved within 1 month in >95% of patients, while C-reactive protein and ferritin normalized within this interval in >80% of patients. Active arthritis persisted at 1 month in 39% of patients, at 3 months in 27%, and at >6 months of followup in 11%. Approximately 60% of patients, including 8 of 10 receiving anakinra monotherapy, attained a complete response without escalation of therapy. Disease characteristics and treatment were similar in partial and complete responders, except that partial responders were markedly younger at onset (median age 5.2 years versus 10.2 years; $P = 0.004$).**

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Associated adverse events included documented bacterial infection in 2 patients and hepatitis in 1 patient. Tachyphylaxis was not observed.

Conclusion. **Anakinra as first-line therapy for systemic JIA was associated with rapid resolution of systemic symptoms and prevention of refractory arthritis in almost 90% of patients during the interval examined. These results justify further study of IL-1 inhibition as first-line, rather than rescue, therapy in systemic JIA.**

Systemic juvenile idiopathic arthritis (JIA) represents ~10% of childhood-onset idiopathic chronic arthritis but contributes disproportionately to arthritis-associated morbidity (1). Chronic arthritis develops in up to 50% of patients with systemic JIA and can be resistant to conventional disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX) and tumor necrosis factor inhibitors (2,3). Even among patients with monophasic disease, systemic inflammation often requires prolonged therapy with high-dose corticosteroids (4,5). Inflammation and corticosteroid therapy can be devastating to the growing skeleton, frequently leading to osteoporosis, pathologic fractures, and permanent loss of stature (6,7). Among children with systemic JIA who receive ongoing care into adulthood, joint replacement has been required in up to 75% (7,8). Therapeutic advances that minimize corticosteroid exposure and prevent the development of chronic arthritis are therefore urgently required.

Recent work has led to an appreciation of interleukin-1 (IL-1) as a critical cytokine for the pathogenesis of systemic JIA. IL-1 antagonism with anakinra (recombinant human IL-1 receptor antagonist) can be strikingly effective in achieving control of systemic symptoms such as fever and rash (9–13). In contrast, established systemic JIA is often less responsive, with many patients exhibiting an unsatisfactory response to anakinra (10–12). Reported experience has been largely restricted to patients with disease refractory to conventional therapy, typically with a history of years of disease (9–12). The question remains whether initiation of IL-1 blockade in the earliest phase of disease, before arthritis has become well established, could be an effective therapeutic approach in children with systemic JIA.

To address this question, we reviewed the clinical outcomes of patients at our centers who received anakinra as part of initial DMARD therapy for systemic JIA. The goals were to determine whether anakinra was effective and safe in this context, to seek predictors of therapeutic response, and to investigate whether early use of anakinra was associated with a more tractable disease course than that documented in the reported experience with systemic JIA.

PATIENTS AND METHODS

Study design. Participating centers were recruited via a series of 3 messages posted to a worldwide pediatric rheumatology list server in early 2010. Investigators committed to providing clinical data on all patients from their centers who met the following entry criteria: 1) clinical diagnosis of systemic JIA, 2) treatment with anakinra as part of the initial DMARD regimen, and 3) initiation of anakinra therapy with interpretable clinical followup before June 1, 2010. There were no exclusion criteria. Prior or concomitant therapy with corticosteroids and/or nonsteroidal antiinflammatory drugs (NSAIDs) was permitted, as was simultaneous (within 2 weeks) initiation of any DMARD in addition to anakinra. The duration between onset of systemic JIA and initiation of anakinra therapy was not restricted. The diagnosis of systemic JIA was established according to the International League of Associations for Rheumatology (ILAR) criteria (14), with the exception that arthritis need not have been present for 6 weeks if therapy was initiated within this time frame. Since the ILAR criteria have limited sensitivity for new-onset disease (15), cases failing to meet the revised criteria were reviewed by a panel of 3 attending pediatric rheumatologists (excluding the submitting physician) and admitted if the diagnosis was considered "highly probable" by unanimous vote.

Case record review and data synthesis. Clinical data were obtained by chart review using a standard data collection form in accordance with a detailed manual of operations (both available upon request from the corresponding author). The following information was abstracted: demographics, clinical phenotype, results of laboratory studies, therapy, adverse events, and response. Physicians were asked to specify why anakinra was chosen as first-line therapy. Active arthritis was defined using established criteria (14). Macrophage activation syndrome was defined as an acute episode of illness characterized by some combination of fever, hepatosplenomegaly, lymphadenopathy, cytopenias, hepatitis, intravascular coagulation, and neurologic impairment (16).

Given concern that available data might not suffice for standard outcome criteria (17,18), we defined responses in advance as complete (no or minimal residual symptoms, with no requirement for supplementary agents to maintain clinical remission and normal laboratory study findings), absent (no or minimal clinical benefit), and partial (intermediate between complete and absent response). For outcomes at given time intervals, patients were considered to have evaluable data if information was available at the time point ±7 days or if data were consistent at time points before and after the point of interest. Except as specified otherwise, data were available on at least 95% of patients for each variable reported. Normal ranges used were as follows: C-reactive protein (CRP) ≤0.5 mg/dl, erythrocyte sedimentation rate (ESR) <20 mm/hour, ferritin <320 ng/ml, platelet count 198–371 × 10^3

cells/μl. Deidentified data were forwarded to the coordinating center (Children's Hospital Boston) for compilation and statistical analysis. Data collection and management were accomplished in compliance with the requirements of the Institutional Review Board at each institution.

Statistical analysis. Continuous variables were compared using the Mann-Whitney U test and are expressed as the median and interquartile range (IQR). Proportions were compared using Fisher's exact test. In this exploratory analysis, *P* values less than 0.05 were considered significant, without correction for multiple comparisons. Significant univariate predictors of complete response were entered into multivariate logistic regression (SPSS software, version 18.0) to identify independent predictors of complete response.

RESULTS

Patients. Forty-six patients (59% of whom were female) met the entry criteria (Table 1). These included 14 who had arthritis for a duration of <6 weeks before resolution and 3 whose disease did not meet the modified ILAR criteria but who were adjudicated to have systemic JIA for the purposes of this research (1 patient with arthralgias without frank arthritis and 2 patients with a first-degree family history of psoriasis; these 3 patients otherwise had typical systemic JIA). One patient whose systemic JIA had been in remission for years without therapy presented with a relapse; all but 1 of the remaining patients presented at or near the beginning of their disease course. Seven patients have previously been described (12,19,20); in most cases their course is described here with at least 1 year of additional followup. According to the enrolling physicians, 36 (78%) were white, including 4 Hispanics, 2 were Asian, 6 were African American, 1 was native North American, and 1 was of other ethnic origin. The study population was similar to recently described cohorts of patients with systemic JIA (5,15).

Treatment. Therapeutic approaches included anakinra alone (22%), anakinra plus DMARDs without corticosteroids (11%), anakinra plus corticosteroids

Table 1. Characteristics of the study population*

	Anakinra alone	Anakinra + DMARDs (no steroids)	Anakinra + steroids (no DMARDs)	Anakinra + steroids + DMARDs	Total
Patients, no. (%)	10 (21.7)	5 (10.9)	21 (45.7)	10 (21.7)	46
Demographic features					
Female, %	50	40	67	60	58.7
Age at onset of systemic JIA, median (range) years	9.7	11.7	7.2	5.7	7.6 (0.75–15.7)
Time from onset to receiving anakinra, median (IQR) days	135	45	150†	46.5†	82.4 (44–172.5)
Duration of observation after receiving anakinra, median (IQR) months	12.5	16.0	15	17.2	14.5 (7.5–26)‡
Concomitant NSAID therapy, %	90	80	67	70	73.9
Clinical features (ever)					
Fever, %	100	100	100	100	100
Evanescent erythematous rash, %	100	100	100	100	100
Arthritis, %	90	100	100	100	97.8
Generalized lymph node enlargement, %	50	0	33.3	20	30.4
Hepatomegaly/splenomegaly, %	10	20	33.3	20	23.9
Serositis, %	0	20	23.8	50	23.9
Macrophage activation syndrome, %	20	0	19	40	19.6
Peak count of joints with active disease, median (IQR)	5.5	7.0	4.0	3.0	5 (3–8)
Pretreatment laboratory features, median (IQR)					
Peak ESR, mm/hour	78	106	80	110	82.5 (55–112)
Peak CRP, mg/dl	10.5	15.1	18.9	17.2	15.3 (10.1–25.6)
Peak white blood cell count, $\times 10^3/\mu$l	21.9	15.3	23.1	22.8	20.8 (16.4–28.3)
Peak absolute neutrophil count, $\times 10^3/\mu$l	13.3	11.2	16.6	17.5	15.7 (12.2–63.5)
Lowest hematocrit, %	30.0	31.0	30.2	29.2	30.1 (27.3–34.5)
Representative peak platelet count, $\times 10^3/\mu$l	431.0	469	569	599	526 (427–713)
Peak ferritin, ng/ml	1,200	1,824	2,673	1,190	1,998 (450–5,872)

* Ranges and interquartile ranges (IQRs) are omitted from subgroups for clarity. DMARDs = disease-modifying antirheumatic drugs; JIA = juvenile idiopathic arthritis; NSAID = nonsteroidal antiinflammatory drug; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
† $P < 0.05$ versus the remaining patient population.
‡ The range of observation duration was 0.75–55 months. The median duration of receiving anakinra was 13.2 months (IQR 6.5–25.7 months; range 0.17–55 months).

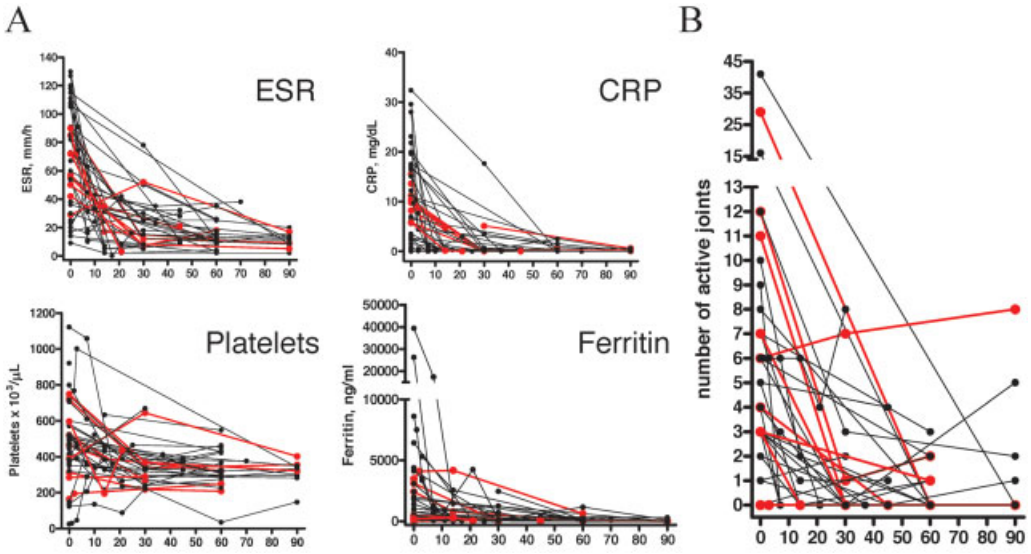

Figure 1. Clinical response in the first 3 months of therapy with anakinra. **A,** Laboratory parameters. **B,** Numbers of joints with active disease. Red lines indicate 10 patients who received anakinra without accompanying corticosteroids or disease-modifying antirheumatic drugs. Numbers on the x-axis refer to days after initiation of anakinra. ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

without other DMARDs (46%), and anakinra plus DMARDs plus corticosteroids (22%). With the exception of 3 patients who received cyclosporine, the DMARD used was MTX, which was given at a median initial dosage of 0.5 mg/kg/week (60% subcutaneously). Twenty percent of patients received intravenous pulse corticosteroids, and 74% received concomitant NSAIDs. Few demographic and clinical differences were observed between any subgroup and the remaining group as a whole (Table 1).

Factors contributing to the choice of anakinra as first-line therapy included the belief that anakinra could be superior to other DMARDs (98% of patients), family willingness to undertake injections (91%), family willingness to consider unorthodox approaches (80%), steroid dependence or intolerance (26%), and contraindications to other treatment options (7%). In 2 patients, for insurance reasons, anakinra was available for use only because of the presence of macrophage activation syndrome. Among the 7 centers contributing ≥3 patients, 60% of patients on average were treated using a single approach, suggesting that local practice patterns influenced treatment choice.

The median duration between symptom onset and systemic JIA diagnosis was 45 days (IQR 30–90 days). Median lag between diagnosis and initiation of anakinra was 14 days (IQR 0–112 days). In all, the median interval between onset of symptoms and start of anakinra therapy was 82 days (IQR 44–173 days). In 21 patients (46%), anakinra was started within 3 days of diagnosis, and in 32 patients (70%), anakinra was started within 30 days of diagnosis. The median starting dose of anakinra was 1.5 mg/kg/day (IQR 1.1–2.0 mg/kg/day; minimum 0.93 mg/kg/day, maximum 11.2 mg/kg/day), and subsequent dose escalation was required in 24% of patients. Patients requiring dose escalation received a median initial dose of 1.3 mg/kg/day, compared with a median initial dose of 1.6 mg/kg/day in patients who did not (*P* not significant). Among 19 patients who started with a dose <1.5 mg/kg/day, 8 (42%) ultimately required a higher dose. One patient received anakinra twice daily. In most patients, therapy with anakinra could not be interrupted during the term of observation, but recurrent dose escalation (tachyphylaxis) was not observed. At the last followup visit, anakinra had been discontinued for inefficacy in 1 patient, for intolerance in 2, and because of remission in 3; 7 patients could be weaned to dosing every other day, although symptoms returned if the interval exceeded 48 hours.

Clinical response. Clinical response was assessed by laboratory and clinical parameters as well as by the requirement for corticosteroids. Median followup was 14.5 months (IQR 7.5–26 months; minimum 0.75 months, maximum 55 months). Response was classified as complete, partial, or absent (see Patients and Methods), reflecting the combined effect of all therapy. In general,

improvement was rapid and striking. Among the 29 evaluable patients with detailed clinical assessments within the first week of therapy, fever and rash resolved completely in 25 (86%), typically within 1–2 days. By 30 days, fever and rash had resolved in 97% of 36 patients. Markers of inflammation also responded rapidly (Figure 1A). By 30 days, the CRP level had normalized in 84% of 31 patients, the ESR in 63% of 30 patients, the ferritin level in 83% of 26 patients, and the platelet count in 71% of 31 patients. In contrast, articular responses tended to lag. Ongoing synovitis remained in 39% of 31 patients at 30 days, 27% of 30 patients at 3 months, and 15% of 20 patients at 6 months. The majority of patients were free of corticosteroids by 2 months (Figure 2).

Complete response to initial therapy was observed in 59% of patients, while another 39% exhibited a partial response. Anakinra was discontinued in 1 patient (2%) for lack of response. Among partial responders, 3 required subsequent intraarticular corticosteroids, 10 escalated or started new DMARD therapy, and 2 required additional therapy for macrophage activation syndrome (see below).

We hypothesized that incomplete response might be associated with lower anakinra dose, longer lag to therapy, higher clinical severity, or fewer concomitant therapies (corticosteroids or DMARDs). However, none of these hypotheses could be substantiated (Table 2). Complete responders and patients with partial/absent responses had equivalent presenting features and received indistinguishable treatment. Only 2 associations were observed: incomplete responders tended to be younger at onset and to receive a higher initial corticosteroid dose. These parameters correlated strongly with each other, since younger patients received higher corticosteroid doses per kg than did older patients ($r^2 = 0.27$, $P = 0.003$). In multivariate analysis, older age at onset remained the only significant predictor of response, with an adjusted odds ratio (OR) of 1.5 per year of life (95% confidence interval [95% CI] 1.1–2.0); corticosteroid dose was no longer predictive when corrected for age at onset (adjusted OR 0.9 [95% CI 0.2–4.2]).

In exploratory analyses, we examined selected candidate factors as potential confounders for age at onset as a predictor of response, including initial and peak anakinra dose (mg/kg/day), treatment allocation (4 groups from Table 1), lag from onset to initiation of anakinra therapy, CRP, ferritin, absolute neutrophil count, and peak count of joints with active disease. While power was limited by sample size, none of these factors compromised the significance of age at onset,

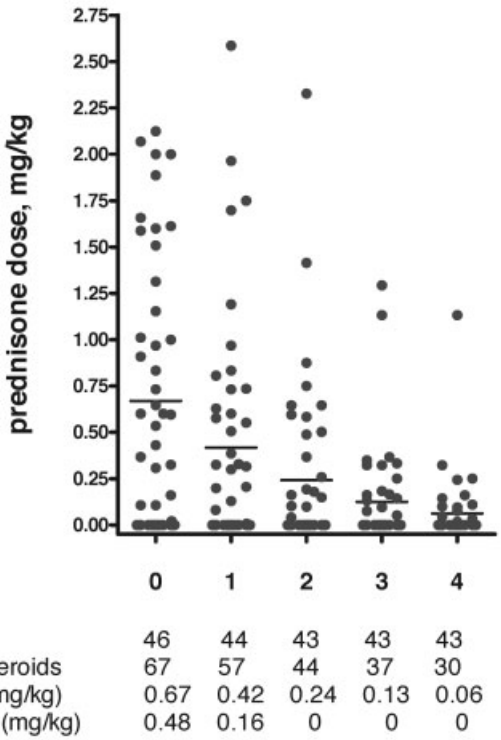

Figure 2. Steroid dosing by month after initiation of anakinra. These values do not include intravenous pulses. Horizontal bar indicates the mean.

which emerged as the sole independent predictor of response in our series. This effect dichotomized optimally at age 7 years; complete response was observed in 75% of patients age ≥7 years, but in only 41% of younger patients ($P = 0.05$).

Anakinra monotherapy. Anakinra was used as the sole disease-modifying agent in 10 patients. The demographic and clinical parameters of this group did not differ markedly from those of the rest of the cohort (Table 1); despite an older median age, this group included our youngest patient (9 months). Of these children, 8 exhibited complete response and required no additional therapy, although 1 required dose escalation to 1.9 mg/kg/day at +4 months. All 8 continued to receive anakinra at a median followup of 12 months. One patient was able to taper to dosing every other day (but no further). Failed tapering attempts in several others suggest that these were not patients who would otherwise have experienced a benign monophasic course. Two patients required additional therapy. The first demonstrated a complete response to anakinra as assessed by clinical examination and markers of inflammation at +1 month, but presented at +5 months with the first of

2 episodes of macrophage activation syndrome (see below). The second had received 7 months of NSAID therapy for fever and rash before anakinra at 1.5 mg/kg/day was initiated because of the onset of polyarthritis. The arthritis responded incompletely to anakinra, including dose escalation to 1.9 mg/kg/day, requiring several months of steroids starting at +3 months to obtain remission. Overall, anakinra alone was able to control both arthritis and systemic clinical features in 8 of 10 children with new-onset systemic JIA.

Persistent arthritis. Chronic arthritis associated with systemic JIA can be resistant to therapy, including IL-1 antagonists (10–12). We hypothesized that early intervention with anakinra might forestall the establishment of chronic arthritis. Among 35 patients followed up for at least 6 months, 31 (89%) had arthritis remission without known chronic joint injury at a median 14 months of followup, while 4 (11%) had active synovitis affecting 1–6 joints at a median 12 months of followup. These 4 included 1 patient who had developed persistent arthritis 15 months prior to initiation of anakinra. Excluding this patient, therapy prevented the development of persistent synovitis in 31 of 34 patients (91%).

Macrophage activation syndrome. Macrophage activation syndrome is a potentially life-threatening complication of systemic JIA and has been reported in patients receiving anakinra (10–12). We observed 11 episodes of macrophage activation syndrome in 9 patients (20%), including 6 at presentation and 5 while they were receiving anakinra. In the 6 patients presenting with macrophage activation syndrome, anakinra was initiated together with corticosteroids in 5 patients and DMARD therapy in 3 (cyclosporine in 2 patients, cyclosporine/MTX/intravenous immunoglobulin in 1 patient). One patient had coronary artery dilation, a known complication of systemic JIA (21), which resolved gradually under therapy. A 4-year-old girl requiring intensive care for macrophage activation syndrome received anakinra monotherapy at a dose of 11.2 mg/kg/day intravenously (5.6 mg/kg every 12 hours). She improved dramatically, but her response remained partial, and at the last followup visit, she was requiring anakinra at 2.3 mg/kg/day, abatacept, and monthly pulse corticosteroids (22). A 7-year-old boy admitted to the hospital because of macrophage activation syndrome received anakinra at 1 mg/kg/day for 3 days followed by 2 mg/kg/day for another 2 days, together with corticosteroids. Fevers persisted, and anakinra was discontinued because of an inadequate response (this patient was the single nonresponder, although some improvement in laboratory parameters had been noted). Altogether, anakinra was considered an effective part of therapy for macrophage

Table 2. Predictors of therapeutic response*

	Complete response	Partial/absent response	*P*	Total
Patients, no. (%)	27 (59)	19 (41)	–	46
Demographic features				
Female, %	55.6	63.2	0.76	58.7
Age at onset of systemic JIA, median (IQR) years	10.2 (6.6–14.3)	5.2 (2.3–8.3)	0.004	7.6 (4.1–12.6)
Treatment parameters				
Initial anakinra dose, median (IQR) mg/kg/day	1.6 (1.1–1.9)	1.5 (1.2–2.2)	0.66	1.5 (1.1–2.0)
Time from onset to receiving anakinra, median (IQR) days	90 (44–150)	75 (30–255)	0.84	82.4 (44–172.5)
Initial corticosteroid dose, median (IQR) mg/kg/day	0.16 (0–0.97)	0.83 (0.32–1.89)	0.03†	0.57 (0–1.23)
Concomitant treatment, %				
NSAIDs	77.8	68.4	0.51	73.4
No corticosteroids, no DMARDs	29.6	10.5	0.16	21.7
DMARDs with or without corticosteroids	29.6	36.8	0.75	32.6
Corticosteroids with or without DMARDs	59.3	79.0	0.21	67.4
DMARDs + corticosteroids	18.5	26.3	0.72	21.7
Clinical parameters, median (IQR)				
Peak ESR, mm/hour	85 (72–113)	70 (52–111)	0.30	82.5 (55–112)
Peak CRP, mg/dl	15.3 (8.5–29.5)	16 (9.2–19.4)	0.53	15.3 (10.1–25.6)
Peak white blood cell count, $\times 10^3/\mu$l	21.0 (17.8–28.0)	20.1 (15.7–28.7)	0.89	20.8 (16.4–28.3)
Peak absolute neutrophil count, $\times 10^3/\mu$l	15.9 (10.4–12.3)	15.7 (10.4–19.5)	0.43	15.7 (12.2–63.5)
Lowest hematocrit, %	30.2 (27.4–36)	30 (26.3–33.4)	0.42	30.1 (27.3–34.5)
Representative peak platelet count, $\times 10^3/\mu$l	569 (425–700)	521 (436–739)	0.81	526 (427–713)
Peak ferritin, ng/ml	3,008 (373–9,429)	1,329 (579–3,240)	0.39	1,998 (450–5,872)
Peak count of joints with active disease	4.5 (3–10)	5 (3–8)	0.71	5 (3–8)

* See Table 1 for definitions.
† $P = 0.08$ excluding patients with a steroid dose = 0 mg/kg. Odds ratio corrected for age at onset was not significant, per multivariate analysis (see Results).

activation syndrome in 5 of 6 patients, consistent with a recent series that also included 2 of our cases (20).

Macrophage activation syndrome was observed on 5 occasions in 4 patients after initiation of anakinra: 1) a patient receiving anakinra at 1.2 mg/kg/day who abruptly discontinued steroids 2 weeks into therapy; 2) a patient receiving anakinra at 1.3 mg/kg/day who developed Epstein-Barr virus infection 4 months into therapy; 3 and 4) a patient receiving anakinra monotherapy at 1.6 mg/kg/day who developed 2 episodes of macrophage activation syndrome at +5 and +8 months without an identifiable trigger—this patient was treated with cyclosporin A and corticosteroids (anakinra was withheld for 2 days during the second episode but was then restarted); and 5) a patient who had presented with macrophage activation syndrome and who had received corticosteroids, cyclosporine, and anakinra at 1.6 mg/kg/day—this patient developed a second episode on day +18 that responded to corticosteroids and anakinra at 2.2 mg/kg/day. While the role of anakinra as a trigger for these 5 cases cannot be determined, in no case was permanent discontinuation necessary. Further, dose escalation often seemed to help control macrophage activation syndrome. Nevertheless, these 11 instances indicate that anakinra at 1–2 mg/kg/day is not invariably sufficient to prevent macrophage activation syndrome in systemic JIA.

Adverse events. Injection site reactions occurred in 44% of the 45 patients with evaluable data, leading to permanent discontinuation of drug in 1 patient and transient discontinuation in several others. There were 3 cases of serious infection. A 4-year-old child treated with anakinra at 1 mg/kg/day and 6 weeks of corticosteroids developed pneumococcal bacteremia at +2 months in the setting of parainfluenza infection. Anakinra was withheld for 1 week but was restarted because of rising levels of markers of inflammation. The patient remained well during an additional 6 months of observation. An 11-year-old child treated with anakinra (1.2 mg/kg/day) and high-dose oral corticosteroids developed an infection at a healed gastric feeding tube site. Anakinra was withheld for 2 weeks but was ultimately escalated to 1.9 mg/kg/day without further complication during 21 additional months of observation. A 3-year-old child receiving anakinra at 1.7 mg/kg/day was admitted to the hospital for several days with pneumonia. No organism was cultured. Anakinra was restarted after discharge.

Other events noted included 2 episodes of bronchitis in 1 patient and recurrent viral respiratory illness in another. Eosinophilic hepatitis required discontinuation of therapy in an 8-year-old patient receiving anakinra at 1.5 mg/kg/day; this case has been described in detail elsewhere (19). Elevation of liver enzymes under anakinra treatment was noted in 2 additional patients, but therapy could be continued. Finally, a 9-month-old infant developed mild asymptomatic neutropenia (absolute neutrophil count 500 cells/μl) which resolved with alternate-day dosing. One child receiving corticosteroids and anakinra at 1.4 mg/kg/day inadvertently received the live measles-mumps-rubella vaccine without evident harm.

DISCUSSION

In this report, we have detailed the real-world experience of 11 centers in 4 countries with anakinra as first-line therapy in systemic JIA. We find that anakinra is associated with generally positive outcomes when initiated early in disease, before arthritis has become well established, in most cases avoiding protracted corticosteroid therapy and forestalling the development of severe, therapy-resistant arthritis.

These findings represent a sharp divergence from the reported natural history of systemic JIA. While 11–42% of systemic JIA patients have a monophasic disease course, generally without development of sequelae (4,5), approximately one-half experience chronically active arthritis resulting in structural joint injury, and one-third develop Steinbrocker class III/IV disability (6,8,23–36) (Table 3). Since children with ongoing medical needs are more likely to remain in contact with providers, these data likely overestimate negative outcomes. Nevertheless, it is remarkable that <10% of 34 patients in our cohort who received anakinra prior to the development of chronic synovitis, and for whom we had posttreatment data for >6 months of followup, displayed active arthritis at last review; of 20 patients for whom we had data at the 6-month time point (corresponding to 7–8 months on average since symptom onset), arthritis remained in only 15%. These outcomes cannot be ascribed to anakinra alone, since most patients also received other agents. However, they compare favorably with data from reported series, in which active arthritis was documented to persist in 36–63% of children 6–9 months after disease onset (5,24,30,31,37). Further, by 4 months after initiation of anakinra (5–6 months of disease), only 30% required corticosteroid therapy. While some series have found comparable rates, the most recent prospective series showed that 69% of children with systemic JIA still received corticosteroids 6–9 months after the start of illness (5,31,37).

Table 3. Outcome series in systemic juvenile idiopathic arthritis*

Author, year (ref.)	No. of subjects	Followup†	Patients with active disease at followup, %	Outcome
Schaller and Wedgwood, 1972 (24)	32	Mean 5.7	59	25% with debilitating arthritis
Calabro et al, 1976 (25)	20	Mean 15	20	15% with Steinbrocker class III/IV
Stoeber, 1981 (26)	209	Mean 15	NR	43% with Steinbrocker class III/IV
Mozziconacci et al, 1983 (27)	72	Minimum >7	NR	67% with injury seen on radiography, 37% with Steinbrocker class III/IV
Svantesson et al, 1983 (28)	33	Median 10	49	45% with joint injury after 10 years
Ansell, 1987 (29)	30	Fixed 10	30–43	>50% with deforming skeletal injury
Schneider et al, 1992 (30)	38	Fixed 2	NR	32% with destructive arthritis
Lomater et al, 2000 (4)	80	Mean 10.7	42.5	29% with Steinbrocker class III/IV
Spiegel et al, 2000 (31)	111	Mean 7.7	NR	22% with moderate-to-severe disability
Minden et al, 2002 (32)	30	Median 16.5	53	NR
Oen et al, 2002 (8)	49	Mean 10.5	55	≥35% with joint injury after 2 years, 60% with arthroplasty by 10 years
Bowyer et al, 2003 (6)	95	Fixed 5	NR	75% with injury seen on radiography
Fantini et al, 2003 (33)	88	Mean 10.9	67.1	NR
Sandborg et al, 2006 (34)	70	Fixed 2	NR	21% with injury seen on radiography
Singh-Grewal et al, 2006 (5)	45	Mean 4.8	NR	36% with active arthritis at 6-month followup
Russo and Katsicas, 2008 (35)	47	Minimum >2	NR	38% with joint injury
Bloom et al, 2009 (36)	31	Mean 8.8	NR	33% with joint injury
Oen et al, 2010 (37)	26	Fixed 6–9 months	>40	69% with corticosteroid therapy at 6–9-month followup

* NR = not reported.
† In years, except where indicated otherwise.

Given this divergence from reported outcomes, it is important to consider whether our results might reflect deliberate or inadvertent selection bias for patients destined for a milder course. Physicians might have chosen anakinra only for their less worrisome patients. Patients/families must have been willing to perform daily injections and have had access to adequate health insurance. These factors could bias toward an older, better educated, and potentially more compliant population. Indeed, the median age of our patients at disease onset, 7.6 years, was higher than that reported in some series (approximately equal to 6 years) but equivalent to that reported in others (5,15,28,30,31,37).

However, we doubt that selection fully explains our favorable results. Disease characteristics at presentation have proven uninformative as to the long-term course of systemic JIA, leaving failure to respond to therapy within 3–6 months as the only factor prognostic of poor outcome (5,30,31,34,36). It is therefore unlikely that we could have chosen only good-prognosis patients for anakinra therapy. In particular, age has proven unreliable as a determinant of outcome; indeed, in 1 series, younger age was found to be associated with a shorter disease course (38). Moreover, many of our patients received anakinra after therapy with NSAIDs and/or corticosteroids had failed, and several only because they presented with macrophage activation syndrome. Finally, among patients in whom tapering of anakinra was attempted, it was generally unsuccessful, suggesting that these patients would have had active disease in the absence of effective therapy. Therefore, it is improbable that patient selection accounts entirely for the divergence between our results and reported experience.

Not all patients exhibited a complete response to anakinra. In ~40% the response was partial, although residual benefit was often substantial, as indicated by the decision to continue injections in all but 1 patient. Comparing complete and partial responders, we observed that patient age, rather than clinical severity, correlated best with the efficacy of treatment (Table 2). In our series, children younger than 7 years were less likely to exhibit a complete response to anakinra-based therapy than those ages 7 years and older (41% versus 75%; $P = 0.05$), despite higher initial corticosteroid dosing. The basis for this difference remains unknown. It is possible that the biology of the disease is different in younger children. However, pharmacokinetic data suggest a trend toward lower anakinra serum levels in children ages 3–6 years receiving 1 mg/kg/day than in older children or adults (39). Therefore, a potential explanation for poorer responses in younger children is that they require a higher dose per kg to achieve similar effective levels (younger and older children received the same median mg/kg/day dose; data not shown). Such a possibility would fit well with the recent observation that

younger patients with autoinflammatory diseases also require higher doses of anakinra (40). However, this hypothesis remains to be tested.

Our report includes a remarkable series of 10 patients treated with anakinra monotherapy for new-onset systemic JIA, with results similar to those of a prospective series recently presented in abstract form (41). Among 10 patients, 9 experienced a complete response, although 1 required months of therapy and a dose escalation to achieve this result and another developed macrophage activation syndrome at +5 months. To the extent that patients treated with anakinra monotherapy were similar to the group as a whole (Table 1), it may be that other patients could have experienced similar responses had they been treated in the same way.

Our experience with anakinra compares favorably with recent series in which children with systemic JIA received anakinra years into the clinical course of their disease (10–12). Since only half of patients responded well, it was proposed that systemic JIA might in fact contain 2 biologically distinct subgroups, only 1 of which is dependent on IL-1 (10). Our data suggest a different interpretation. We find that the large majority of systemic JIA patients treated with anakinra soon after disease onset experience marked clinical benefit, if not invariably complete disease control, implicating IL-1 in the pathogenesis of most cases of systemic JIA. Indeed, 9 of 10 patients treated with anakinra monotherapy demonstrated at least transient clinical and laboratory remission of disease. Rather, we speculate that IL-1 blockade may be less effective in established disease. This might be because effective blockade is difficult to achieve in the chronically inflamed joint, where sources of IL-1 (macrophages, neutrophils, mast cells, platelet microparticles) are present in abundance. Alternatively, cytokines such as IL-17 could begin to drive arthritis independently of IL-1, as observed in 1 murine model (42). Whatever the explanation, our findings suggest that IL-1 remains of central importance in most cases of systemic JIA in its earliest phase.

Anakinra was generally well tolerated in our patients. Injection site reactions were common but required permanent discontinuation in only 1 patient. In another patient, therapy was stopped because of eosinophilic hepatitis. Macrophage activation syndrome was observed in 4 patients receiving anakinra, but in no case did we observe clear evidence for a causal association, and all patients could ultimately continue therapy. Of greatest concern, several patients developed bacterial infection, although all could safely restart anakinra. Whether these infections represented chance events or were the result of anakinra-induced immunocompromise is difficult to determine. Some reassurance may be drawn from the relative safety of anakinra in adult rheumatoid arthritis and in overt bacterial sepsis (43,44). The safety of long-term anakinra use in systemic JIA remains unknown, a caveat of importance since few of our patients could discontinue therapy.

Our study has a number of limitations. Since this was a retrospective series, we cannot fully account for the effect of patient selection. Comparison of our results with those in the literature is intrinsically compromised by differences in demographics, followup, and measures of outcome. Further, since anakinra has only recently come into widespread use in systemic JIA, the duration of patient observation was limited to a median of 14.5 months, leaving open the possibility that favorable early responses may not translate into durable therapeutic success. In particular, while none of our patients required recurrent escalation of anakinra dosing, tachyphylaxis to this agent has been observed anecdotally and could compromise long-term efficacy (45).

Taken together, our results lend support to the use of IL-1 blockade early in the course of systemic JIA. Treatment was associated with brisk improvement in systemic inflammatory features and an unexpectedly low incidence of chronic, treatment-refractory arthritis. Further, anakinra obviated the need for corticosteroids in many patients and was associated with the ability to taper steroids rapidly in others, potentially reducing the morbidity commonly associated with treatment for systemic JIA. We therefore suggest that anakinra is a promising option for first-line DMARD therapy in systemic JIA and that it should be studied in greater detail to establish definitively the efficacy and long-term safety of this approach.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Nigrovic had full access to all of

the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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