Etanercept Treatment in Patients with Refractory Systemic Onset Juvenile Rheumatoid Arthritis

YUKIKO KIMURA, PAULO PINHO, GARY WALCO, GLORIA HIGGINS, DONNA HUMMELL, ILONA SZER, MICHAEL HENRICKSON, SANDRA WATCHER, and ANDREAS REIFF

ABSTRACT. ***Objective***. To assess the efficacy and safety of etanercept in a large cohort of children with refractory systemic onset juvenile rheumatoid arthritis (SOJRA).

Methods. Standardized questionnaires were sent to US pediatric rheumatologists about patients with SOJRA treated with etanercept. Data were collected at baseline and at the last visit on etanercept. Response to treatment was assessed and compared to baseline as the mean percentage reduction in the following: acute phase reactants, prednisone dose, active joint count, and physician global assessment of disease activity. Response was defined as poor if the mean reduction was < 30%, fair if 30% to < 50%, good if 50% to < 70%, and excellent if > 70%.

Results. We analyzed data obtained by survey of 82 SOJRA patients treated with etanercept for a mean of 25 months. Poor response to treatment was observed in 45% of the children, fair response in 9%, good in 13%, and excellent in 33%. Baseline steroid therapy could be discontinued in 27/59 (46%) patients. One or more disease flares occurred in 45% of all patients. Twenty-nine patients (35%) discontinued therapy, mostly due to lack of response or flare. There were 32 adverse event reports, most not considered serious, except for 2 cases of macrophage activation syndrome.

Conclusion. In this cohort of children with SOJRA, 46% had a good or excellent response, and most were able to reduce concomitant corticosteroid doses. The response to etanercept was fair or poor in more than half our study population, and disease flares were common. Due to the unique cytokine profile of SOJRA, tumor necrosis factor blockade may not be the optimal therapeutic approach for children with treatment-resistant SOJRA. (J Rheumatol 2005;32:935–42)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS — SYSTEMIC ONSET
ANTI-TUMOR NECROSIS FACTOR THERAPY — ETANERCEPT

The systemic onset subtype of juvenile rheumatoid arthritis (SOJRA), which makes up about 20% of all patients with JRA[1], is characterized by prominent extraarticular features such as quotidian fevers, evanescent rash, and frequently serositis, organomegaly and lymphadenopathy. SOJRA patients present a therapeutic challenge, as more than 80% have a polyphasic or chronic persistent disease course[2,3], more than 50% have a poor outcome, and, unlike other forms of JRA, SOJRA is associated with an increased risk of mortality (2.8–14%)[3-5]. In addition, the majority of children with JRA who experience longterm disability (Steinbrocker functional class III or IV) have SOJRA[6].

Traditional treatment for SOJRA includes nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, and methotrexate (MTX)[1,7]. However, an estimated 40–50% of SOJRA patients are refractory to these standard therapies and require alternative agents such as cyclosporine[8,9], cyclophosphamide[10], thalidomide[11], or biologic response modifiers[7,12,13]. However, even with these therapies, many SOJRA patients continue to require longterm corticosteroid therapy for disease control, which is associated with significant toxicity. Attesting to the severity of disease and the difficulty of treating SOJRA is the fact that 85% of all JRA patients who have undergone stem cell transplant for arthritis had SOJRA[14]. Hence, newer, more effective, and less toxic therapeutic alternatives are urgently needed for this particular form of JRA.

Tumor necrosis factor (TNF) and other proinflammatory cytokines have been implicated in the pathogenesis of JRA. Etanercept, a soluble TNF receptor fusion protein, was found to be safe and effective in a multicenter randomized placebo controlled trial in MTX-resistant or intolerant patients with polyarticular-course JRA[15,16]. The efficacy of etanercept specifically in SOJRA, however, has not been

From Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center, Hackensack, New Jersey; Children's Hospital, Columbus, Ohio; Vanderbilt University, Nashville, Tennessee; Children's Hospital of San Diego, San Diego, California; Children's Hospital Central California, Madera, Calfornia; and Children's Hospital of Los Angeles, Los Angeles, California, USA.

Y. Kimura, MD; P. Pinho, MD; G. Walco, PhD, Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center; G. Higgins, PhD, MD, Children's Hospital, Columbus; D. Hummell, MD, Vanderbilt University, Nashville; I. Szer, MD, Children's Hospital of San Diego; M. Henrickson, MD, Children's Hospital Central California; S. Watcher RN; A. Reiff, MD, Children's Hospital of Los Angeles.

Address reprint requests to Dr. Y. Kimura, Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center, 30 Prospect Avenue, Hackensack, NJ 07601. E-mail: ykimura@humed.com

Accepted for publication December 2, 2004.

reported in any large series. Several studies have suggested that although initially promising, etanercept may not be as effective a treatment for SOJRA compared to other types of JRA. The initial study of etanercept in polyarticular course JRA[15] included 22 SOJRA patients who did not have active systemic disease upon entering the study. Seventeen of these SOJRA patients (77%) qualified as responders after 3 months' etanercept treatment in the open label phase of the trial and continued on to the randomized phase. During this latter blinded phase, 7 of the 8 (88%) SOJRA patients randomized to placebo flared, but in addition, 4 of 9 patients (44%) who had continued etanercept also flared. In contrast, only 18% of patients with other onset types of JRA who had continued on active drug experienced a disease flare. In the longterm open label followup study[16], where 12 of the 48 JRA patients remaining in the study had SOJRA, only 47% of SOJRA patients (using an intent-to-treat analysis) achieved a 70% improvement, compared to 62% of other onset types.

A recent study by Quartier, *et al* analyzed the efficacy of etanercept separately in 22 SOJRA patients compared to 39 patients with other types of JRA, and they also found that SOJRA patients were less likely to respond[17]. Two small single-center studies of 4 and 9 SOJRA patients, respectively, also suggested a poor response to this agent in these patients[18,19]. A prospective study conducted in 10 patients with adult-onset Still's disease showed that treatment with etanercept resulted in an American College of Rheumatology 50% response in only 4 patients, even when higher doses (25 mg three times per week) were used[20]. Only one of the 3 patients with active systemic features had improvement of these features, and none experienced improvement in their arthritis.

In addition to the question of efficacy, the safety of etanercept has been of particular concern in SOJRA. These patients have a propensity to develop macrophage activation syndrome (MAS), a potentially fatal hemophagocytic syndrome[21,22], often triggered by medications[23,24]. Etanercept has been described as a treatment for MAS in one case report[25], while another recent report linked the initiation of etanercept to the development of MAS[26].

Our objective was to gather information on a large cohort of SOJRA patients in order to determine whether etanercept is an effective and safe treatment for SOJRA. Additionally, we hoped to identify disease characteristics that may be helpful in predicting response to treatment.

MATERIALS AND METHODS

Initial and followup questionnaires on the use of etanercept in patients with SOJRA were sent to 122 pediatric rheumatologists in the US. Information was collected on a total of 100 SOJRA patients who were treated with etanercept, of whom 82 had analyzable data. Twenty-nine pediatric rheumatology centers contributed a mean of 3.45 (range 1–24) patients each. Patients were excluded for the following reasons: lost to followup (2), followup period of less than 3 months (3), and incomplete data sets (13). Characteristics of all patients are shown in Table 1.

Collected information included demographic data (sex, age, age at disease onset, disease duration at the time of etanercept introduction), doses of concomitant medications (NSAID, prednisone, MTX, cyclosporine, cyclophosphamide), presence of joint pain and systemic symptoms (defined as fever, serositis, or rash), laboratory markers of disease activity [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, and white blood count (WBC)], active joint count (number of joints with swelling, or if no swelling is present, number of joints with limitation of motion accompanied by heat, pain, or tenderness), and the physician global assessment of disease activity on a 100 mm visual analog scale. Timepoints included the start of etanercept therapy and last followup while taking etanercept. Other information included response time, whether higher doses of etanercept were used, information about disease flares while on therapy, adverse events, discontinuation of therapy, and the reason for discontinuation.

Response was measured as percentage decrease from baseline in: (1) prednisone dose, (2) active joint count, (3) laboratory markers of disease activity (ESR, CRP, or platelet count), and (4) physician global assessment of disease activity score. To be included in the data analysis, each patient had to have complete data for at least 3 of the variables for at least 2 timepoints, including at least one of the laboratory measurements of disease activity as stated above. Patients who did not have ESR values for both timepoints were required to have values for either the CRP (n = 9) or the platelet count (n = 6). Patients who were not taking prednisone at baseline were required to have data for the 3 other response variables at both timepoints. In addition, a followup period of at least 3 months of etanercept therapy was required. Overall response was measured as an average of the percentage decrease in these variables. Patients were defined as excellent responders if the average was $\geq$ 70%, good if the average was 50% to < 70%, fair if the average was 30% to < 50%, and poor if the average was < 30%. Although there is no accepted definition of disease flare in SOJRA, patients in this study were considered to have a flare if they developed active systemic features (fevers, rash, or serositis) and/or an increased number of swollen joints associated with worsening in available laboratory indicators of disease activity, such as ESR, CRP, WBC count, or platelet count, that necessitated either an increase in the prednisone dose, the institution of intravenous pulse methylprednisolone, intraarticular corticosteroid injections, or initiation of a new disease modifying agent.

Although the ACR Pediatric score has been validated as a tool to measure response in JRA patients[27], it was not used in this study because some measures, such as the Childhood Health Assessment Questionnaire and patient/parent assessment of well being, were not retrospectively available. We defined the ability to decrease prednisone as a measure of improvement (expressed as percentage decrease in dose from baseline), since a large number of patients with SOJRA require longterm chronic corticosteroid therapy, and a decrease in dose would be an important measure of improvement for these patients.

Statistical analysis. SPSS 11.5 was used for the statistical analysis. A number of outcomes are purely descriptive and thus no formal analyses were conducted. When comparisons were made between the outcome groups, analyses of variance (ANOVA) were used when outcome variables were rational, and nonparametric statistics, including logistic regression, were used when outcomes were binary or categorical.

RESULTS

Demographic data. Of the 82 patients included in the analysis, 48 (59%) were female (Table 1). The mean age at disease onset was 4.25 ± 3.73 years (range 0.25–17), and the mean disease duration prior to initiation of etanercept was 5.18 ± 4.2 years (range 0–19.9). One patient was older than 16 at disease onset (17 years old). By definition, this makes him a patient with adult-onset Still's disease rather than SOJRA, but because the 2 diseases are virtually identical

Table 1. Patient characteristics at baseline.

	Study Patients, (n = 82)	Excluded Patients, (n = 18)
No. female (%)	48 (59)	8 (44)
Mean age at onset, yrs, ± SD (range)	4.25 ± 3.73 (0.25–17)*	5.1 ± 3.43 (2.2–16.5)*
Mean age at baseline, yrs	9.44 ± 5.04 (0.58–23.67)*	8.67 ± 3.68 (3.8–18)*
Mean disease duration at baseline, yrs	5.18 ± 4.2 (0–19.9)*	4.33 ± 3.11 (0.6–7.5)*
Percentage of patients taking prednisone	73	89
Percentage of patients taking MTX	76.8	83.3
Mean no. of active joints (range)	16 ± 15.9 (0–56)*	10.2 ± 9.2 (2–34)*
Mean physician disease activity score, mm (range)	64.6 ± 23 (7.2–100)*	75 ± 21 (24–100)*

* Values are mean ± SD (range).

aside from the difference in ages at onset, we included him in the analysis.

Duration and dose of etanercept. The mean duration of etanercept treatment for all patients at last followup was 24.8 ± 12.3 months (range 3–70). The duration of treatment was > 6 months in 79 patients, and > 12 months in 69. All patients initially received the standard dose of 0.4 mg/kg (maximum 25 mg) etanercept twice weekly subcutaneously. However, 29 patients (35%) received a higher dose subsequently during their treatment course. The mean dose of etanercept in these patients was 0.83 ± 0.24 (range 0.6–1.4) mg/kg/dose.

Response to etanercept. Overall, there was a decrease in the number of patients with systemic symptoms (from 45 at baseline to 21 at last followup) and joint pain (76 to 45, respectively), but the difference was not significant and may reflect the natural disease course rather than response to therapy (Table 2). Among all patients, the mean active joint count (16 to 8.8), ESR (52.5 to 34.2 mm/h), and physician global assessment of disease activity score (64.6 to 32.36 mm) all decreased significantly (all p = 0.0001) throughout the observation period. The total number of patients taking prednisone also decreased significantly from 59 to 32 (p = 0.003) as did the overall mean dose of prednisone, from 0.47 to 0.26 mg/kg/day (p = 0.01).

Thirty-seven patients had no or poor response (mean response < 30%), 7 had a fair response (30% to < 50%), while 11 had a good response (50% to < 70%), and 27 had an excellent response (≥ 70%) (Figure 1). Sex and age at onset did not significantly influence response to treatment. There was a tendency for poor responders to have had a longer disease duration at baseline, but this difference did not reach statistical significance (Table 3). There was no significant relationship between the presence of systemic symptoms and response to etanercept. Systemic symptoms and disease activity measures (physician global assessment of disease activity score, active joint count, prednisone dose, and acute phase reactants) were not significantly different at baseline among responder groups (Figure 1). Because the "good" and "fair" responder groups contained too few patients (n = 7 and n = 11, respectively) and had insufficient power (0.10 to 0.45) to analyze separately, these 2 intermediate responder groups were combined to assess specific changes pre- and post-etanercept. Repeated measures ANOVA were conducted for all 4 variables. Although overall ANOVA indicated significant time by responder-group interaction effects, post hoc analyses showed no statistically significant differences. This is because a key assumption of the ANOVA model is that variance is similar in all groups, but when our data were examined, the variances in the "poor" outcome group at followup were much greater for all

Table 2. Clinical features of all patients at baseline and last followup.

	Baseline	Last Followup	p
No. with systemic symptoms (%)	45 (54)	21 (26)	0.612
No. with joint pain (%)	76 (93)	45 (55)	0.695
Active joint count*	16 ± 15.9 (0–56)	8.8 ± 14.2 (0–56)	0.0001
ESR (n = 67), mm/h*	52.5 ± 34.2 (5–148)	31.9 ± 27.3 (2–128)	0.0001
CRP (n = 23), mg/l*	13.5 ± 21.8 (0.4–105)	12.3 ± 29.4 (0–143.1)	0.880
Platelets (n = 53) (× 10^3 per mm^3)*	451 ± 128 (226–699)	393 ± 146 (146–862)	0.006
Physician global assessment, mm*	64.6 ± 23 (7.2–100)	36.31 ± 32.36 (0–98)	0.0001
No. taking prednisone therapy (%)	60 (73)	32 (39)	0.003
Prednisone dose, mg/kg/day*	0.47 ± 0.64 (0–3)	0.26 ± 0.61 (0–3)	0.01
Etanercept dose, mg/kg/dose*	0.42 ± 0.7 (0.22–0.76)	0.48 ± 0.22 (0.15–1.3)	NS

* Values are mean ± SD (range). NS: not significant.

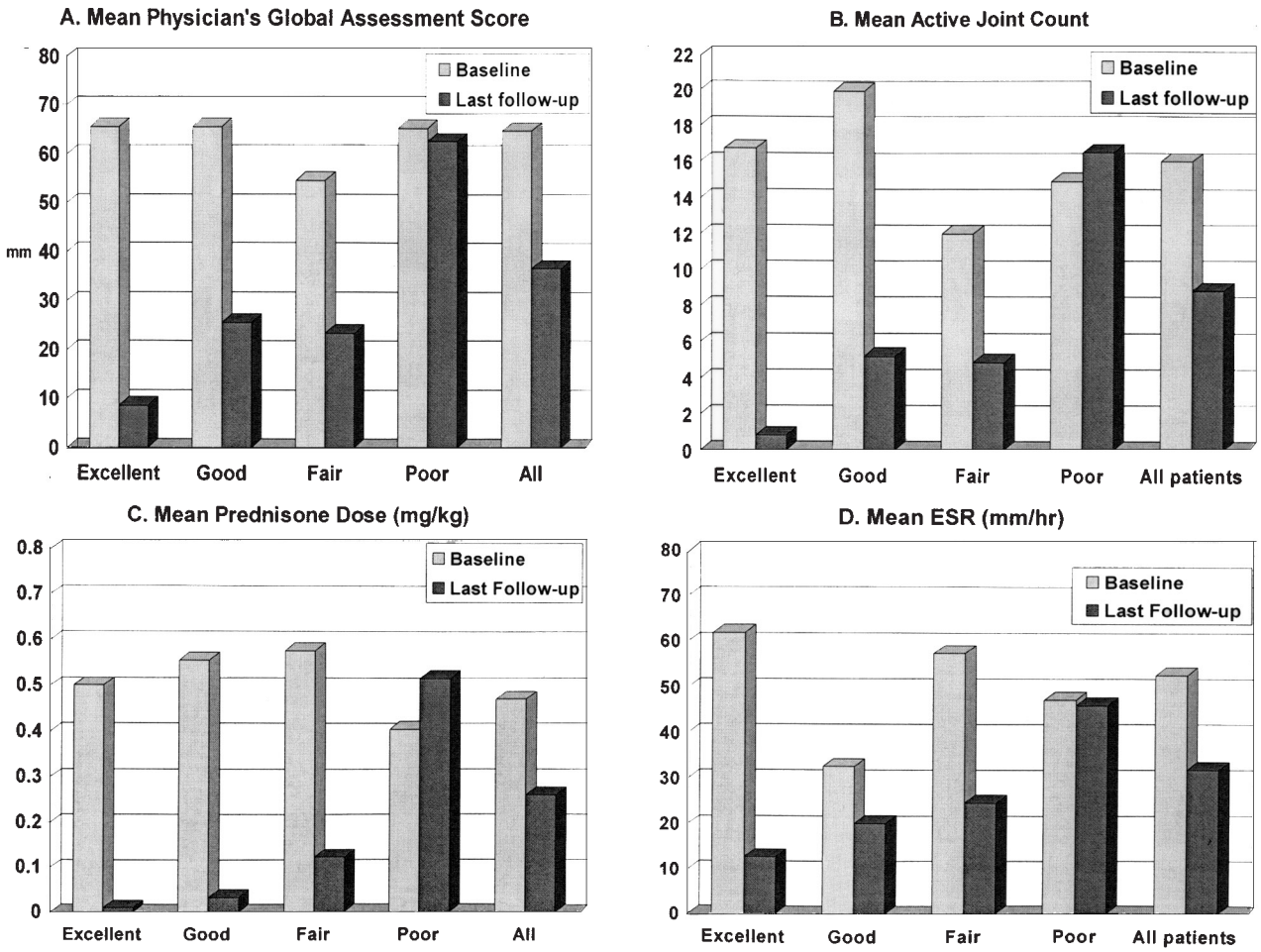

Figure 1. Disease activity measures by response group. A. Mean physician global assessment of disease activity scores at baseline and last followup (mm). B. Mean active joint count at baseline and last followup. C. Mean prednisone dose at baseline and last followup (mg/kg/day). D. Mean ESR at baseline and last followup (mm/h).

Table 3. Characteristics of each response group.

Response	Excellent	Good	Fair	Poor
N (%)	27 (33)	11 (13)	7 (9)	37 (45)
F, n	15	8	3	22
M, n	12	3	4	15
Age at onset, yrs*	4.5 ± 3	4.3 ± 4.6	3.9 ± 2.9	4.2 ± 4.2
Age at baseline, yrs*	9.2 ± 5	8.7 ± 6.8	6.8 ± 4.1	10.3 ± 4.7
Disease duration, yrs*†	4.6 ± 4	4.4 ± 3.8	2.9 ± 2.5	6.1 ± 4.7
Treatment duration, mo*	26.7 ± 14.2	23.4 ± 12.7	23.8 ± 14.5	23.3 ± 12.2

* Values are mean ± SD. † $p = 0.162$; $F = 1.86$.

4 dependent variables compared to the other responder groups, leading to this outcome (Levene's test of equality of error variances ranged from $F = 8.62$ to $F = 19.24$, all $p < 0.0001$).

Of the patients who discontinued prednisone, 21 were excellent, 7 good, one fair, and 3 were poor responders. Additionally, 3 nonresponders had started taking prednisone at followup. Of the 3 poor responders who were able to discontinue prednisone, one had a severe flare unresponsive to infliximab or the reinstitution of etanercept a year after discontinuing prednisone, the second was able to discontinue prednisone but required intraarticular steroid injections every 3 months, and the third required institution of oral daily cyclophosphamide therapy and cyclosporine in addition to a higher dose of etanercept. The number of patients taking MTX decreased (from 63 to 52), and the number of

patients taking cyclosporine decreased (from 24 to 8). Eight patients were taking cyclophosphamide at baseline. Although 3 of these patients had discontinued it at followup, 2 additional patients had been started on cyclophosphamide therapy.

Concomitant medications. All but 4 patients (2 excellent, one good, and one poor responder) were taking prednisone, MTX, or cyclosporine at baseline, and the majority (78%) of these patients were taking a combination of these agents. In addition, many patients had failed or were intolerant of either MTX or prednisone or both before beginning etanercept. Table 4 lists the concomitant medications taken in each response group at baseline, at last followup, or at any time during the study period. As shown in Table 4, the excellent responders were able to discontinue most background medications, while the poor responders were not able to do so to a significant degree, indicating that discontinuation of background medications did not account for the poor response in most cases. Indeed, the few poor responders who discontinued medications such as MTX, cyclosporine, or cyclophosphamide usually did so because of poor response to those medications.

Based on recent experience from the TEMPO study (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) in patients with RA, showing improved outcome in patients who took MTX and etanercept in combination compared to etanercept or MTX alone[28], we attempted to determine whether patients who took both MTX and etanercept throughout the study period had a better response than those who took etanercept alone. However, the percentages of patients who took the combination of medications were essentially the same in all response groups.

Disease flares and discontinuation of therapy. Thirty-seven patients (45%) were reported to have one or more flares while taking etanercept, not including flares due to an etanercept shortage or temporary discontinuation for other reasons (Table 5). The likelihood of flare was higher in the poor responder group (68%), but flares occurred frequently in all groups, even among the excellent responders (7 of 27 patients, 26%). Altogether, 29 patients (35%) discontinued treatment. Of these, the reason for discontinuation was poor response or flare in 21 (72.4%) (Table 6).

Adverse events. Thirty-two adverse events were reported in a total of 22 patients. The most common adverse event was infection (n = 9). None were serious enough to necessitate hospitalization. Injection site reactions and somatic complaints (fatigue, headaches, myalgias) were the next most common (6 each). Three patients developed mild urticaria and other allergic symptoms, but etanercept was not discontinued. Hypercalciuria and/or kidney stones occurred in 3 patients. The most serious adverse event was macrophage activation syndrome, which occurred in 2 patients. These 2 patients had already been taking etanercept for 12 and 25 months prior to developing MAS, and in both instances MAS occurred during a disease flare. Therefore, investigators concluded that etanercept was not directly implicated in the triggering of MAS. Both children were treated with high-dose corticosteroids, other immunosuppressants, and infliximab to control the MAS, which eventually resolved in both patients. Another patient developed mild myocardial dysfunction and pericarditis during a flare, which persisted after etanercept had been discontinued, indicating it was unlikely to be related to the medication. There was no increase in the rate of adverse events in the patients treated with higher doses.

Table 4. Concomitant medications during study period by response group. Data are n (%).

Response Group	PRD	IVMP	MTX	CSA	CYC	IVIG	IACS	Other
Excellent, n = 27								
At any time	21 (78)	2 (1)	24 (89)	8 (30)	1 (4)	0	1 (4)	1 (4)*
At baseline	21 (78)	2 (1)	23 (85)	8 (30)	1 (4)	0	0	0
At last followup	3 (11)	1 (4)	17 (63)	0	0	0	1 (4)	1 (4)*
Good, n = 11								
At any time	9 (82)	0	8 (73)	3 (27)	1 (9)	0	0	0
At baseline	9 (82)	0	7 (64)	2 (18)	0	0	0	0
At last followup	2 (18)	0	7 (64)	1 (9)	1 (9)	0	0	0
Fair, n = 7								
At any time	5 (71)	1 (14)	6 (86)	3 (14)	1 (14)	0	0	0
At baseline	5 (71)	0	6 (86)	2 (26)	0	0	0	0
At last followup	3 (43)	1 (14)	5 (71)	1 (14)	1 (14)	0	0	0
Poor, n = 37								
At any time	29 (78)	11 (30)	29 (78)	11 (30)	8 (22)	4 (11)	5 (14)	3 (8)†
At baseline	27 (73)	7 (19)	28 (76)	10 (27)	7 (19)	4 (11)	4 (11)	0
At last followup	23 (62)	8 (22)	23 (62)	6 (16)	6 (16)	2 (5)	3 (8)	3 (8)†

PRD: Prednisone; IVMP: intravenous pulse methylprednisolone; MTX: methotrexate; CSA: Cyclosporine; CYC: cyclophosphamide; IVIG: intravenous immune globulin; IACS: intraarticular corticosteroids; * Oral IgG. † Oral IgG, 1 azathioprine, 1 mycophenolate mofetil.

Table 5. Disease flares while taking etanercept therapy.

Response Group	Total Patients, n	No. with 1 or More Flares (%)
Excellent	27	7 (26)
Good	11	2 (18)
Fair	7	3 (43)
Poor	37	25 (68)
Total	82	37 (45)

Table 6. Reasons for discontinuation of etanercept.

Reason	No. Patients
Poor response or flare	21
Poor compliance	4
Remission	3
Adverse event	1
Total	29 (35% of all patients)

DISCUSSION

We obtained data on 82 patients with refractory SOJRA treated with etanercept for an average of over 2 years. The majority of patients (54%) had a poor or limited response, and flares occurred in 45% of all patients. Even among the responders, more than one-quarter had one or more flares while on etanercept therapy. On the other hand, 46% of patients had a good or excellent response, and most of these responders were able to discontinue corticosteroids, which is an important finding in these patients with refractory disease. Etanercept did not prevent the development of MAS during a disease flare in 2 patients, one of whom was initially an excellent responder. By the end of the followup period, one-third of patients had discontinued etanercept, mostly due to lack of efficacy.

Almost all of our study patients had relatively long disease durations prior to the initiation of etanercept (5.18 ± 4.2 yrs), which raises the question whether long-standing disease might decrease the likelihood of response to etanercept. Indeed, patients with a poor response to etanercept had a longer disease duration at the start of therapy, compared to patients who had an excellent response (6.1 vs 4.6 yrs, respectively), although this did not reach statistical significance. None of the other disease characteristics, including the presence of systemic symptoms, differed between the response groups and could be used as predictive indicators.

With respect to etanercept tolerability, our results are similar to those reported by Lovell, *et al*, in the 2 studies of etanercept in patients with polyarticular course JRA[15,16], but contradict the results of Quartier, *et al*, in which serious adverse events were common and led to discontinuation of etanercept in 20% of the study participants[17]. In contrast, only one child in our study discontinued etanercept therapy because of an adverse event, a child with pericarditis and myocardial dysfunction during a disease flare. Although 2 children developed MAS and subsequently discontinued etanercept and started infliximab, etanercept was not thought to be the cause of the MAS. However, that 2 children developed MAS while taking etanercept underscores the failure of etanercept to prevent disease flares in these patients.

Our results are limited by the retrospective survey design of the study. As such, it is subject to ascertainment bias. Additionally, although we asked the participating physicians to record disease flares and other significant events during the entire followup period, we obtained information about these patients only at several timepoints, and so there may have been other flares that were not recorded or validated by the data that were obtained. We were also not able to use the validated JRA core set criteria to measure response. In fact, there are no measures of disease activity or response criteria that have been validated specifically for SOJRA, making assessment of response difficult. Finally, the addition and tapering of background medications, especially corticosteroids, could have affected the assessment of response to etanercept and confounded the results. Despite these limitations, however, our observations are consistent with other recently published studies, such as that of Quartier, *et al*, who found SOJRA patients were less responsive to etanercept and more likely to experience flare compared to patients with other types of JRA[17].

These findings raise the question whether TNF-α blockade is sufficient to control systemic arthritis in children and adults. Although some patients with SOJRA do respond to anti-TNF agents, and elevated levels of TNF-α and other proinflammatory cytokines have been described in the serum and synovial fluid of patients with various forms of JRA[29-31], there is recent evidence that certain cytokines, especially interleukin 6 (IL-6)[32-36] and IL-18[37-39], may play an important role in both the systemic disease and the articular severity of SOJRA[40]. IL-6 is elevated in the serum and synovial fluid of many types of chronic inflammatory arthritis, but appears to be present at much higher concentrations in SOJRA[29,32,41,42], and dramatic responses to anti-IL-6 receptor monoclonal antibody in patients with systemic arthritis have been reported[43-45]. In addition, there have been anecdotal reports and a small open label study of SOJRA patients who appeared to respond to the anti-IL-1 receptor antagonist anakinra, even when they have had a poor response to anti-TNF agents[46,47]. In contrast, there has been contradictory evidence with regard to the role of TNF-α in SOJRA[42,48-50], suggesting that TNF-α blockade may not be the best therapeutic strategy for SOJRA.

We found etanercept was safe and well tolerated in this large cohort of patients with SOJRA followed for an average of more than 2 years. However, these patients appeared to be less responsive to etanercept compared to patients with nonsystemic forms of JRA. Disease flares, even in excellent responders, were common. Clinical trials of agents that tar-

get other cytokines that may be more effective need to be pursued to effectively treat this difficult and disabling disease.

ACKNOWLEDGMENT

We acknowledge the following individuals for contributing patient data: Suzanne Li, Robert Rennenbohm, Alexander Lawton, Carol Wallace, Donald Goldsmith, Deborah Rothman, Barbara Ostrov, Suzanne Bowyer, Daniel Lovell, Leslie Abramson, Gail Cawkwell, Thomas Hahn, Lisa Imundo, Robert Lipnick, Arthur Newman, James Nocton, Linda Ray, and Lawrence Zemel.

REFERENCES

1. Petty RE, Cassidy JR. The juvenile idiopathic arthritides and juvenile rheumatoid arthritis. In: Cassidy JR, Petty RE, editors. Textbook of pediatric rheumatology. 4th ed. Philadelphia: W.B. Saunders; 2001:214-321.
2. Calabro JJ, Holgersson WB, Sonpal GM, Khoury MI. Juvenile rheumatoid arthritis: a general survey of 100 patients observed for 15 years. Semin Arthritis Rheum 1976;5:257-98.
3. Lomater C, Gerloni V, Gattinara M, Mazzotti J, Cimaz R, Fantini F. Systemic onset juvenile rheumatoid arthritis: a retrospective study of 80 consecutive patients followed for 10 years. J Rheumatol 2000;27:491-6.
4. Wallace CA, Levinson JE. Juvenile rheumatoid arthritis: outcome and treatment for the 1990's. Rheum Dis Clin North Am 1991;17:891-905.
5. Ansell BM, Wood PN. Prognosis in juvenile chronic polyarthritis. Clin Rheum Dis 1976;2:397-412.
6. Hafner R, Truckenbrodt H. Course and prognosis of systemic juvenile chronic arthritis — retrospective study of 187 patients [German]. Klin Padiatr 1986;198:401-7.
7. Ilowite NT. Current treatment of juvenile rheumatoid arthritis. Pediatrics 2002;109:109-15.
8. Reiff A, Rawlings E, Shaham B, Franke E, Bernstein B. Cyclosporine: a safe and effective alternative in the treatment of recalcitrant juvenile rheumatoid arthritis (JRA) and juvenile dermatomyositis. J Rheumatol 1997;24:2436-43.
9. Gerloni V, Cimaz R, Gattinara M, Arnoildi C, Pontikaki I, Fantini F. Efficacy and safety profile of cyclosporine A in the treatment of juvenile chronic (idiopathic) arthritis. Rheumatology Oxford 2001;20:907-13.
10. Wallace CA, Sherry DD. Trial of intravenous pulse cyclophosphamide and methylprednisolone in the treatment of severe systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum 1997;40:1852-5.
11. Lehman TJ, Striegal KH, Onel KB. Thalidomide therapy for recalcitrant systemic onset juvenile rheumatoid arthritis. J Pediatr 2002;140:125-7.
12. Murray KJ, Lovell DJ. Advanced therapy for juvenile arthritis. Best Pract Res Clin Rheumatol 2002;16:361-78.
13. Kimura Y, Imundo L, Li S. High dose infliximab in the treatment of resistant systemic juvenile rheumatoid arthritis [abstract]. Arthritis Rheum 2001;44 Suppl:S272.
14. Wulffraat NM, Sander LA, Kuis W. Autologous hemopoietic stem-cell transplantation for children with refractory autoimmune disease. Curr Rheumatol Rep 2000;2:316-23.
15. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 2000;342:763-9.
16. Lovell DJ, Giannini EH, Reiff A, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis; interim results from an ongoing multi-center, open-label, extended treatment trial. Arthritis Rheum 2003;48:218-26.
17. Quartier P, Taupin P, Bourdeaut F, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum 2003;48:1093-101.
18. Higgins GC, Jones K, Rennenbohn RM. Variable response of systemic juvenile rheumatoid arthritis to etanercept [abstract]. Arthritis Rheum 2000;43 Suppl:S257.
19. ten Cate R, van Suijlekom-Smit LW, Brinkman DM, et al. Etanercept in four children with therapy-resistant systemic juvenile idiopathic arthritis. Rheumatology Oxford 2002;41:228-9.
20. Husni ME, Maier AL, Mease PJ, et al. Etanercept in the treatment of adult patients with Still's disease. Arthritis Rheum 2002;46:1171-6.
21. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 2001;85:421-6.
22. Stephan JL, Kone-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur AM. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology Oxford 2001;40:1285-92.
23. Jacobs JC, Gorin LJ, Hannissian AS, Simon JL, Smithwick EM, Sullivan D. Consumption coagulopathy after gold therapy for JRA. J Pediatr 1984;105:674-5.
24. Barash J, Cooper M, Tauber Z. Hepatic, cutaneous and hematologic manifestations in juvenile chronic arthritis. Clin Exp Rheumatol 1991;9:541-3.
25. Prahalad S, Bove KE, Dickens D, Lovell DJ, Grom AA. Etanercept in the treatment of macrophage activation syndrome. J Rheumatol 2001;28:2120-4.
26. Ramana TV, Schneider R. Macrophage activation syndrome following initiation of etanercept in a child with systemic onset juvenile rheumatoid arthritis. J Rheumatol 2003;30:401-3.
27. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
28. Klareskog L, van der Heijde D, de Jager JP, et al, for TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
29. Lepore L, Pennesi M, Saletta S, Perticarari S, Presani G, Prodani M. Study of IL-2, IL-6, TNF-alpha, IF-gamma and delta in the serum and synovial fluid of patients with juvenile chronic arthritis. Clin Exp Rheumatol 1994;12:561-5.
30. Mangge H, Schauenstein K. Cytokines in juvenile rheumatoid arthritis (JRA). Cytokine 1998;10:471-80.
31. Madson KL, Moore TL, Lawrence JM, Osborn TG. Cytokine levels in serum and synovial fluid of patients with juvenile rheumatoid arthritis. J Rheumatol 1994;21:2359-69.
32. de Benedetti F, Massa M, Robbioni P, et al. Correlation of serum IL-6 levels with joint involvement and thrombocytosis in systemic juvenile chronic arthritis. Arthritis Rheum 1991;34:1158-63.
33. Prieur AM, Roux-Lombard P, Dayer JM. Dynamics of fever and the cytokine network in systemic juvenile arthritis. Rev Rhum (Engl Ed) 1996;63:153-70.
34. Pignatti P, Vivarelli M, Meazza C, Rizzolo MG, Martini A, de Benedetti F. Abnormal regulation of interleukin 6 in systemic juvenile idiopathic arthritis. J Rheumatol 2001;28:1670-6.
35. de Benedetti F, Martini A. Is systemic juvenile rheumatoid arthritis an interleukin 6 mediated disease? J Rheumatol 1998;25:203-7.
36. Fishman D, Gaulds G, Jeffery R, et al. The effect of polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102:1369-76.
37. Kawashima M, Yamamura M, Taniai M, et al. Levels of interleukin-18 and its binding inhibitors in the blood circulation of

patients with adult-onset Still's disease. Arthritis Rheum 2001;44:550-60.
38. Kawaguchi Y, Terajima H, Harigai M, Hara M, Kamatani N. Interleukin-18 as a novel diagnostic marker and indicator of disease severity in adult-onset Still's disease. Arthritis Rheum 2001;44:1716-7.
39. Maeno N, Takei S, Nomura Y, Imanaka H, Hokonohara M, Miyata K. Highly elevated serum levels of interleukin-18 in systemic juvenile idiopathic arthritis but not in other juvenile idiopathic arthritis subtypes or in Kawasaki disease: comment on the article by Kawashima, et al. Arthritis Rheum 2002;46:2539-41.
40. de Benedetti F, Pignatti P, Massa M, Sartirara P, Ravelli A, Martini A. Circulating levels of interleukin-1 and of interleukin-1 receptor antagonist in systemic juvenile rheumatoid arthritis. Clin Exp Rheumatol 1995;13:669-84.
41. de Benedetti F, Robbioni P, Massa M, Viola S, Albani S, Marini A. Serum interleukin 6 levels and joint involvement in polyarticular and pauciarticular juvenile rheumatoid arthritis. Clin Exp Rheumatol 1992;10:493-8.
42. Rooney M, David J, Symons J, DiGiovine F, Varsani H, Woo P. Inflammatory cytokine responses in juvenile chronic arthritis. Br J Rheumatol 1995;34:454-60.
43. Iwamoto M, Nara H, Hirata D, et al. Dramatic improvement of intractable adult-onset Still's disease by intravenous humanized anti-interleukin 6 receptor antibody (MRA) [abstract]. Arthritis Rheum 2001;44 Suppl:S118.
44. Yokota S, Miyamae T, Imagawa T, et al. Long-term therapeutic efficacy of humanized anti-IL-6-receptor antibody for systemic juvenile idiopathic arthritis [abstract]. Arthritis Rheum 2002;46 Suppl:S479.
45. Yokata S, Miyamae T, Imagawa T, et al. Phase II trial of anti-IL-6 receptor antibody (MRA) for children with systemic-onset juvenile idiopathic arthritis [abstract]. Arthritis Rheum 2003;48 Suppl:S429.
46. Irigoyen PI, Olson J, Hom C, Ilowite NT. Treatment of systemic onset juvenile rheumatoid arthritis with anakinra [abstract]. Arthritis Rheum 2004;50 Suppl:S437.
47. Henrickson M. Efficacy of anakinra in refractory systemic arthritis [abstract]. Arthritis Rheum 2004;50 Suppl:S438.
48. de Benedetti F, Pignatti P, Massa M, et al. Soluble TNF receptor levels reflect coagulation abnormalities in systemic juvenile chronic arthritis. Br J Rheumatol 1997;36:581-8.
49. Yilmaz M, Kendirli SG, Altinatas D, Bingol G, Antmen B. Cytokine levels in serum of patient with juvenile rheumatoid arthritis. Clin Rheumatol 2001;20:30-5.
50. Ou LS, See LC, Wu CJ, Kao CC, Lin YL, Huang JL. Association between serum inflammatory cytokines and disease activity in juvenile idiopathic arthritis. Clin Rheumatol 2002;21:52-6.