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Efficacy of Etanercept for the Treatment of Juvenile Idiopathic Arthritis According to the Onset Type

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***Objective*. To assess the efficacy of etanercept in patients with juvenile idiopathic arthritis (JIA), and to assess the tolerance of these patients to etanercept.**

***Methods*. All JIA patients with active chronic polyarthritis, who were first treated with etanercept between November 1999 and June 2001 in 18 French centers because of poor response or intolerance to methotrexate, were included in this open-label, prospective, multicenter study. A standardized questionnaire was sent to the treating physicians. We assessed the validated international core-set score for JIA activity every 3 months and performed an intent-to-treat analysis. We also compared the risk of treatment failure in patients defined as having systemic-onset, oligoarticular-onset, or polyarticular-onset JIA.**

***Results*. Sixty-one patients were enrolled and were followed up for a median of 13 months. Treatment had to be stopped in 1 patient who became pregnant and in 12 patients due to severe side effects, including neurologic or psychiatric disorders, retrobulbar optic neuropathy, major weight gain, severe infection, cutaneous vasculitis with systemic symptoms, hemorrhagic diarrhea, uveitis flare, and pancytopenia. All of these side effects disappeared after discontinuation of etanercept. Crohn's disease was subsequently diagnosed in 1 child. Scores improved by ≥30% in 73% of patients after 3 months, but this proportion decreased to 39% after 12 months. The response rate was significantly lower in patients with systemic-onset JIA than in those with oligoarticular- or polyarticular-onset JIA.**

***Conclusion*. Treatment of JIA with etanercept may be associated with a wide spectrum of severe side effects. Although most patients initially respond to etanercept, this initial response is not always followed by sustained improvement over longer periods of time. In addition, the higher rate of treatment failure in the group with systemic-onset JIA indicates that these patients in particular may require alternative treatments.**

Juvenile idiopathic arthritis (JIA) represents several conditions that are characterized by early-onset arthritis (before age 16 years) that persists in one or more joints for at least 6 weeks, and in which infectious arthritis and other well-defined illnesses have been actively excluded (1). Most of these conditions were formerly known as juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis. JIA may be associated with severe disability and life-threatening complications, particularly in patients in whom polyarthritis develops and who do not respond satisfactorily to treatment (2). Patients in whom polyarthritis develops are usually treated with methotrexate, 0.2–1.0 mg/kg of body weight weekly (3,4). Other disease-modifying or immunosuppressive drugs often are less effective or are not toler-

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ated. The use of systemic corticosteroids must be restricted because of their adverse effects, particularly on growth. However, methotrexate is not always well tolerated and has only a moderate effect on the prevention of disability (5).

The latest classification of the International League of Associations for Rheumatology (ILAR) distinguished 7 groups of JIA according to the following: 1) the onset pattern (systemic, and oligoarticular or polyarticular with no systemic symptoms); 2) the presence or absence of rheumatoid factor in polyarticular JIA; 3) a personal or family history of psoriasis, which defines psoriatic JIA; and 4) the presence of enthesitis, sacroiliitis, HLA–B27, or other features that define enthesitis-related JIA (1). The type of onset is the best predictor of methotrexate efficacy. Patients with systemic-onset JIA tend to respond poorly to methotrexate, whereas those with oligoarticlular-onset JIA in whom polyarthritis develops secondarily are more likely than other JIA patients to respond to methotrexate (5–7).

Etanercept, a soluble tumor necrosis factor (TNF) receptor fusion protein that binds and inactivates TNFα and lymphotoxin α, is effective and well tolerated in patients with rheumatoid arthritis (RA) (8). Results of a multicenter pediatric trial performed in the US demonstrated that etanercept was effective and well tolerated in 74% of children (n = 69) with JRA and polyarthritis, regardless of the type of disease onset (9).

In November 1999, we initiated a prospective, open-label, multicenter study to assess the efficacy of and tolerance to etanercept in children with JIA and a polyarticular course who responded poorly to methotrexate. We also compared the efficacy of treatment in patients from the 3 different onset groups.

PATIENTS AND METHODS

Patients. The inclusion criteria were as follows: 1) JIA according to the ILAR criteria (1), 2) "active" chronic polyarticular disease, as defined by the presence of $\geq$5 swollen joints and $\geq$3 joints with pain and limitation of motion for at least 6 months, regardless of the type of onset of JIA, and 3) intolerance to or lack of efficacy of methotrexate at a dosage of at least 0.4 mg/kg of body weight weekly. Written informed consent was obtained from all patients or their parents (for those younger than age 18 years).

The exclusion criteria were as follows: 1) other major concurrent diseases, 2) ongoing infection or requirement for a live attenuated vaccine, 3) uncontrolled severe systemic symptoms and/or biologic features of macrophage activation syndrome (serum fibrinogen level $<$1 gm/liter, cytopenia, hypertriglyceridemia), 4) abnormal liver function, with hepatic aminotransferase concentrations more than double the normal value for age, 5) low white blood cell, neutrophil, or platelet count, 6) radiologic evidence of destructive, nonreversible polyarthritis (Steinbrocker class III or IV) (10), and 7) familial and social conditions rendering regular medical assessment impossible. Pregnancy was also an exclusion criterion, and young women or girls who were at risk of becoming pregnant were required to use contraception.

Patients who were using nonsteroidal antiinflammatory drugs or corticosteroids were required to have received stable doses of these medications for at least 1 month before initiation of etanercept treatment. Disease-modifying and immunosuppressive drugs, including methotrexate, had to be withdrawn at least 15 days before the initiation of etanercept treatment, unless justification was provided by the patient's physician. Each case was analyzed by an independent medical expert before agreement for inclusion was given.

Study design. The patients received subcutaneous etanercept (Enbrel; Wyeth Lederle, Paris la Défense, France), 0.4 mg/kg of body weight (maximum 25 mg) twice per week. The first injections were systematically administered at the hospital. One of the parents (and the patient, when possible) was taught how to administer the injections, so that the subsequent injections were administered at home, sometimes with the assistance of a nurse. A standardized questionnaire was sent to each treating physician in order to collect the following data prospectively: the patient's previous medical history, physical symptoms, number of swollen joints, number of joints with limitation of motion, tenderness, or pain, the score obtained using the validated French version of the Childhood Health Assessment Questionnaire (CHAQ) (11), the physician's and parent's global assessment of disease activity, and the parent's assessment of pain, using a visual analog scale.

Physical examination, laboratory tests (including standard hematologic and serum chemistry analyses), and disease activity assessment were performed at the time of enrollment, on day 1 of etanercept treatment (before administration of etanercept), every month for the first 3 months, and every 3 months thereafter. Physical examinations and disease activity assessment had to be performed every time in every patient by the same physician, who could be the treating physician. Tolerance to etanercept was systematically recorded. The levels of antinuclear antibodies (ANA) and anti–double-stranded DNA (anti-dsDNA) antibodies were measured upon enrollment and every 3 months thereafter. ANA was measured by indirect fluorescence on HEp-2 cells. For measurement of anti-dsDNA, Farr radioimmunoassay was used in the main center and in 3 other institutions, enzyme-linked immunosorbent assay was used in 11 centers, and immunofluorescence on *Crithidia luciliae* was used in 3 centers.

The disease was considered to have improved by 30%, 50%, or 70% if at least 3 of the 6 indicators of disease activity improved by at least 30%, 50%, or 70% with respect to baseline, and if no more than 1 indicator worsened by 30% or more (12). As in the study by Lovell et al (9), the following indicators of disease activity were used: the number of joints with limitation of motion not due to deformity, the number of "active" joints (i.e., joints with swelling not due to deformity or joints with limitation of motion plus pain, tenderness, or both), the CHAQ score, global assessment of disease activity by the

Table 1. Baseline characteristics of patients according to type of JIA onset*

	Type of JIA onset			
	Systemic	Oligoarticular	Polyarticular	All patients†
No. of patients	22	24	13	61
Sex, females/males	13/9	21/3	13/0	49/12
Age, mean years (range)	12 (4–22)	10 (5–16)	12 (5–17)	12.2 (4–22)
Disease duration, mean years (range)	6.2 (2–14)	7.7 (2–13)	5.1 (1–11)	6.6 (1–17)
Previous treatments				
No. (%) using corticosteroids	22 (100)	16 (67)	11 (85)	49 (80)
Cumulative no. of months, median (range)	63 (5–259)	17 (0–154)	17 (0–132)	44 (0–259)
No. (%) using methotrexate	22 (100)	24 (100)	13 (100)	61 (100)
No. (%) using other disease-modifying drugs	15 (68)	7 (29)	3 (23)	27 (44)
Disease activity parameters				
No. of active joints, mean	22	11	15	16
No. of joints with limitation of motion, mean	31	22	28	26
Physician global assessment score, mean	51	48	49	50
Patient/parent global assessment score, mean	46	48	42	46
CHAQ score, mean	2.15	1.64	1.46	1.81
Erythrocyte sedimentation rate, mean mm/hour	50	39	42	44
Treatments maintained after initiation of etanercept				
No. (%) using methotrexate	4 (18)	4 (17)	2 (15)	10 (16)
No. (%) using prednisone	22 (100)	11 (46)	11 (85)	44 (72)
Prednisone dosage, mean mg/kg of body weight daily (range)	0.25 (0.1–1.9)	0.11 (0–1.3)	0.17 (0–0.5)	0.19 (0–1.9)

* Twelve patients in the systemic-onset group had intermittent systemic symptoms (e.g., fever <38.5°C or mild skin rashes) at the time of initiation of etanercept. Thirteen patients in the oligoarticular-onset group had antinuclear antibodies, and 6 had developed uveitis. Five patients in the polyarticular-onset group had either antinuclear antibodies (n = 3) or rheumatoid factor as assessed by the latex and Rose-Waaler tests (n = 2); 1 patient in this group had developed uveitis, and 1 patient had a "dry" polyarthritis with diffuse joint involvement and little swelling. Physician and patient/parent global assessment scores were based on a visual analog scale ranging from 0 (best) to 100 (worst). The Childhood Health Assessment Questionnaire (CHAQ) was scored from 0 (best) to 3 (worst). JIA = juvenile rheumatoid arthritis.
† Includes 2 patients with psoriatic JIA who are classified separately from the 3 main groups.

physician, global assessment of disease activity by the patient or the patient's parent, and the erythrocyte sedimentation rate. Disease flare was defined by at least 30% worsening of 3 or more of the 6 response indicators with respect to the last assessment, with at least 2 active joints. The end point of data collection was June 2002.

Statistical analysis. The primary end point was defined as improvement of the score for JIA activity (core-set score) of at least 30%. Secondary end points were defined as improvement of the core-set score by either 50% or 70%. Treatment failure was defined as the absence of improvement of the core-set score or as treatment intolerance leading to discontinuation of etanercept. The analysis was performed at 3, 6, 9, and 12 months. Logistic regression models adjusted for age, disease duration, and value of the 6 indicators of the core set of criteria for JIA activity prior to inclusion were used to explore the association between the end point and the type of JIA onset. Because the data were repeated measures for each child, the hypothesis of independence of these measures could not be retained. Thus, a longitudinal data analysis was performed, using a marginal logistic model for correlated responses (13). The evolution of each item of the core-set score at month 3 was presented as descriptive data. All of the tests were two-sided, and the 5% significance level was used. Analyses were performed using SAS version 8.1 software (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the patients and treatments. The study group comprised 61 patients with JIA, from 18 centers (Table 1). One center included 28 patients, 3 centers included 3–6 patients, and 14 centers included 1 or 2 patients. JIA was diagnosed before age 13 years in all cases, but 5 patients were older than age 18 years when etanercept treatment was initiated. In all 24 of the patients with oligoarticular-onset JIA, extended arthritis (with involvement of at least 5 joints) had developed before etanercept treatment was initiated. The 2 patients with psoriatic JIA were so classified because they had a history of psoriatic skin lesions in addition to polyarthritis and ANA positivity. None of the other 59 patients had a personal or familial history of psoriasis. All of the patients had previously been treated with methotrexate, which either was not tolerated (gastrointestinal intolerance developed in 4 patients, and 1 patient experienced a major increase in hepatic aminotransferases) or had failed to control the disease activ-

ity. In 46 patients, methotrexate had been administered at doses higher than 0.4 mg/kg/week (up to 1.0 mg/kg/week). Other treatments that had been administered previously included cyclosporine (n = 12), pulsed intravenous methylprednisolone (n = 6), D-penicillamine (n = 4), hydroxychloroquine (n = 4), sulfasalazine (n = 3), azathioprine (n = 3), gold salts (n = 3), intravenous immunoglobulin (n = 3), and cyclophosphamide (n = 1).

Methotrexate treatment was continued in 10 patients despite treatment with etanercept (Table 1), at dosages higher than 0.4 mg/kg/week in 4 patients. These patients had tolerated methotrexate well, and their physicians expected combined therapy to be more effective than etanercept alone. Methotrexate was reintroduced between 2.5 and 6 months after the onset of etanercept therapy in 4 other patients (2 with systemic-onset, 1 with oligoarticular-onset, and 1 with polyarticular-onset JIA). Etanercept had previously been well tolerated in these patients but did not affect disease activity.

Duration of etanercept treatment. Etanercept was administered for periods ranging from 18 days (it was discontinued early, before completing 1 month of treatment, in 3 patients, due to a severe adverse event) to 30 months (median 13 months). Thirty-one patients completed at least 12 months of treatment, and their data were available every 3 months. Treatment was stopped within 3 months in 4 patients due to intolerance. Treatment was stopped after 3–6 months in 9 patients, after 6–9 months in 8 patients, and after 9–12 months in 5 patients, due to intolerance or lack of efficacy. In addition, no data were available for 1 patient at 6 months and for 4 patients at both 9 months and 12 months. Among patients for whom data were available, we calculated the proportion of those who continued to receive etanercept, at several time points (Figure 1). Data following 15–30 months of treatment were available for 24 patients, including 4 patients with systemic-onset JIA, 12 with oligoarticular-onset JIA, 7 with polyarticular-onset JIA, and 1 with psoriatic JIA. Four of these 24 patients stopped using etanercept during the second year due to either intolerance, disease flare, or the patient's decision after long-lasting remission of inflammation.

Tolerance to etanercept. Etanercept was withdrawn in 1 patient who became pregnant and in 12 patients (20%) due to severe side effects, which occurred in 10 patients (16%) before the end of the first year. Other patients experienced minor to moderate side effects, most of which occurred within the first 3 months of treatment and spontaneously resolved (Table 2). The

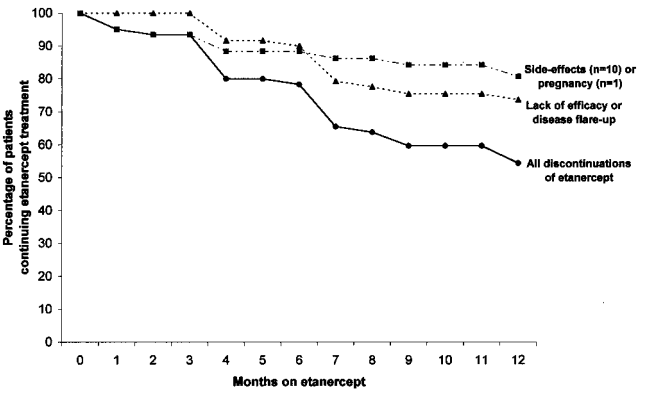

Figure 1. Percentage of patients continuing etanercept treatment over time, by reason for discontinuation (side effects or pregnancy, lack of efficacy or flare, and total).

rate of severe adverse events did not differ according to the type of JIA onset, regardless of whether patients with systemic-onset JIA had systemic symptoms at the onset of etanercept treatment. Adverse events occurred in 4 of 22 patients with systemic-onset JIA, 5 of 24 with oligoarticular-onset JIA, 2 of 13 with polyarticular-onset JIA, and 1 of 2 patients with psoriatic arthritis. Only 1 of the patients who experienced severe adverse events was receiving methotrexate, which had been reintroduced shortly before the occurrence of an appendicular abscess.

The weight gain observed in 2 teenaged girls was not associated with diabetes or intolerance to carbohydrates. One of these 2 patients had also gained a large amount of weight 3 years previously (while receiving methotrexate), and the other girl was receiving combination oral contraceptives. In the 2 patients who had uveitis flare, withdrawal of etanercept and local corticosteroid therapy resulted in a marked improvement. In one 8-year-old patient with a 5-year history of typical ANA-positive extended oligoarticular JIA, severe bloody diarrhea and abdominal pain developed 18 days after initiation of etanercept therapy. In this patient, the symptoms resolved within 2 weeks of stopping treatment and recurred after the first injection when etanercept was reintroduced, which led to definitive withdrawal of the treatment. Results of an intestinal biopsy performed in that patient were characteristic of Crohn's disease. In the other patients, the symptoms completely resolved within a few days or weeks of discontinuation of etanercept.

In the 1 patient who had macrophage activation syndrome, reintroduction of etanercept after 2 months was well tolerated. In 2 other patients, the ANA con-

Table 2. Main side effects and unexpected events during etanercept therapy in patients with juvenile idiopathic arthritis (JIA)*

	No. of patients	JIA onset type	No. of months receiving etanercept
Events that justified etanercept withdrawal			
Pancytopenia	2	Both systemic-onset	0.5, 12†
Severe psychiatric disorders	2	Both oligo-onset	3, 3
Uveitis flare	2	Poly-onset, oligo-onset	12, 12.5
Retrobulbar optic neuropathy	1	Oligo-onset	3
Headaches and marked dysesthesia	1	Poly-onset	14
Hemorrhagic diarrhea (revealing Crohn's disease)	1	Oligo-onset	0.5
Vasculitic skin rash + systemic symptoms	1	Systemic-onset	0.5
Major weight gain (20 kg)‡	1	Psoriatic	9
Appendicular abscess and weight gain (6 kg)§	1	Systemic-onset	7
Pregnancy (1 month)¶	1	Systemic-onset	2
Events that resolved spontaneously			
Mild reactions at injection site	17	7 systemic-onset, 5 oligo-onset, 5 poly-onset	1–9
Cutaneous rash	10	4 systemic-onset, 2 oligo-onset, 4 poly-onset	<2 months
Mild gastrointestinal disorders	10	5 systemic-onset, 3 oligo-onset, 2 poly-onset	<2 months
Headaches	7	3 oligo-onset, 4 poly-onset	2–6
Mild mood changes	6	4 systemic-onset, 2 oligo-onset	1–9
Asthenia, anorexia	2	1 systemic-onset, 1 oligo-onset	3, 3
Thoracic pain	1	Systemic-onset	2
Chronic cough	1	Poly-onset	5
Hematoma	1	Oligo-onset	3

* Oligo-onset = oligoarticular-onset; poly-onset = polyarticular onset.
† One of these patients had macrophage activation syndrome; etanercept was successfully reintroduced 2 months later.
‡ Patient had gained a large amount of weight 3 years previously, while receiving methotrexate.
§ Occurrence while patient was receiving methotrexate, which had been reintroduced 2 months previously, and a combination oral contraceptive.
¶ No obstetric complication; patient had a healthy 9-month-old child at last followup.

centration rose from 1:128 and 1:256, respectively, to >1:30,000, with the presence of low levels of anti-dsDNA antibodies. Etanercept was discontinued after 5 or 6 months in both patients, due to a lack of efficacy. Minor increases in ANA concentrations were observed in 12 other patients, but these patients did not have any other laboratory evidence of autoimmune disease. Minor infections developed in several patients during etanercept therapy, most of which affected the upper respiratory tract. Treatment was interrupted for 10 days to 2 weeks in 5 patients, which resulted in increased pain and stiffness until etanercept was reintroduced.

Effect of etanercept on JIA activity. A 30% improvement of the core-set score was achieved in 73% of patients at month 3 but in only 39% at month 12. Complete results for 50% and 70% improvement for each time point are shown in Table 3. Only 2 of the patients who had improved by less than 30% by 3 months had improved by at least 30% by 6 months. In both patients, the improvements lasted fewer than 3 months. Figure 2 provides a description of each item included in the core-set score, and shows the percentage of patients who improved by at least 30% at month 3, according to the type of JIA onset.

Within the first year of treatment, 9 patients (4 with systemic-onset, 2 with oligoarticular-onset, and 3 with polyarticular-onset JIA) experienced a disease flare. These patients had an increase in the number of inflamed joints and a deterioration of most of the other parameters of disease activity. In addition, 3 patients with systemic-onset JIA also experienced systemic symptoms. Among 24 patients who were treated with etanercept for ≥15 months and for whom data were available, 2 had a disease flare after 18 or 19 months, and 3 had no or only minimal improvement of JIA activity. The other 19 patients had an improvement of 30–70% from baseline after a median followup of 21 months.

Table 3. Effect of etanercept on juvenile idiopathic arthritis activity

Improvement in core-set score, from baseline	Percentage of patients improved*			
	Month 3	Month 6	Month 9	Month 12
≥30%	73	61	51	39
≥50%	54	52	44	35
≥70%	38	33	33	26

* By intent-to-treat analysis.

Response to etanercept according to JIA onset. Multivariate analyses showed that systemic-onset JIA was associated with a significantly higher risk of not achieving 30% improvement during the entire period compared with oligoarticular-onset or polyarticular-onset JIA ($P = 0.0002$ and $P = 0.0031$, respectively). Differences in response to treatment were observed at each time point (Table 4). The risk of not achieving 50% or 70% improvement was also significantly greater in patients with systemic-onset JIA compared with those with oligoarticular-onset JIA, for the entire period ($P < 0.0001$ and $P = 0.0008$, respectively). The risk of not reaching 50% or 70% improvement did not differ significantly between patients with systemic-onset JIA and those with polyarticular-onset JIA at any of the time points. There was no significant difference in any of the analyses between patients with oligoarticular-onset JIA and those with polyarticular-onset JIA, regardless of the degree of improvement of the core-set score.

Outcome of patients treated with a combination of etanercept and methotrexate. Eight of the 10 patients who continued receiving methotrexate following initiation of treatment with etanercept improved by at least 30% at 3 months. In 4 of these patients, improvement was still present at the time of the last followup (after 12–30 months). Two of the 4 patients who restarted methotrexate after the initiation of etanercept showed an improvement of the disease that persisted after 6–24 months of followup.

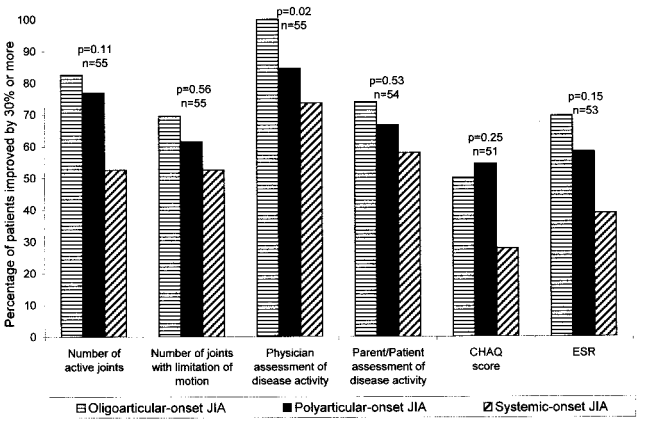

Figure 2. Percentage of patients who achieved at least 30% improvement at 3 months, for each of the constitutive items of the core-set score, according to the type of onset of juvenile idiopathic arthritis (JIA). Results were derived from the relationship between the changes in each item of the core-set (adjusted according to the baseline value of the item), as continuous variables, and the type of JIA. The differences between the values at month 3 and at baseline were computed. CHAQ = Childhood Health Assessment Questionnaire. ESR = erythrocyte sedimentation rate. *P* values were determined by Fisher's exact test.

Table 4. Differences in response to etanercept between the 3 JIA onset groups*

Time point	JIA onset		
	P, systemic vs. oligoarticular	*P*, systemic vs. polyarticular	*P*, polyarticular vs. oligoarticular
Month 3	0.0056	0.0265	0.64
Month 6	0.0364	0.0497	0.92
Month 9	0.0016	0.0276	0.29
Month 12	0.0014	0.0194	0.29
1-year followup period	0.0002	0.0031	0.54

* JIA = juvenile idiopathic arthritis. *P* values were determined by multivariate analysis.

Changes in corticosteroid dosages following initiation of etanercept treatment. The dosage of corticosteroids was progressively tapered in the 30 patients who were receiving oral prednisone or prednisolone at the time of etanercept initiation and who improved by at least 30% after 3 months. Between the third and the sixth months of etanercept therapy, the median dosage of prednisone or prednisolone was reduced from 0.22 mg/kg/day (range 0.08–0.59) to 0.10 mg/kg/day (range 0–0.34) in the 26 patients for whom these data were available. The dosage was further reduced after the sixth month, and only 6 patients who continued etanercept at month 12 were still receiving corticosteroid treatment. Disease flares or loss of efficacy of etanercept occurred in 5 patients in whom corticosteroid doses had been reduced (in 3 patients between months 3 and 6, and in 2 patients between months 9 and 12).

We compared the reduction in the dosage of corticosteroids between the third and the sixth months in the 11 patients with systemic-onset JIA, 9 with oligoarticular-onset JIA, and 6 with polyarticular-onset JIA for whom data were available. There were no significant differences between the 3 groups of patients.

Outcome of patients in whom etanercept was stopped. Ten of the 30 patients in whom etanercept was withdrawn had a disease flare within the following month.

DISCUSSION

We studied 61 patients with JIA who were treated with etanercept and followed up for a median of 13 months. Although most patients initially responded to

etanercept therapy, discontinuation of treatment because of intolerance or loss of efficacy markedly reduced the percentage of patients who experienced sustained improvement after 1 year. In addition, patients with systemic-onset JIA were less responsive to etanercept treatment than were other JIA patients.

The frequency of severe adverse effects in our patients was higher than that expected from previous studies of series of adults and children treated with etanercept for rheumatic diseases (8,9,14–17). However, the small number of patients in our study and the absence of a control group mean that this difference should be interpreted with caution. All of the adverse effects we observed were probably related to etanercept administration, because they disappeared after treatment withdrawal. Moreover, most of these complications, including severe infections (18,19), uveitis flares (20), psychiatric disorders (9,21), neurologic disorders, and retrobulbar optic neuropathy (21), have been previously reported in patients treated with etanercept.

The occurrence of Crohn's disease in one of our patients was unexpected, because anti-TNFα therapy has been successfully used to treat this disease, including in children (22). Because Crohn's disease may sometimes present with arthritis, it is debatable whether this patient should have been reclassified as having Crohn's disease rather than JIA. However, etanercept was introduced in this patient because of a long history of typical extended oligoarticular-onset JIA beginning in early childhood. In addition, the gastrointestinal symptoms that developed after initiation of etanercept treatment resolved after treatment withdrawal and reappeared after its reintroduction. This and the occurrence of skin vasculitis in another child are consistent with the fact that etanercept may result in autoimmune and inflammatory disorders in some patients (23–28). In addition, laboratory evidence of autoimmunity, such as the increase of ANA levels reported here, is frequently observed (9,15,29). However, the safety of etanercept has been assessed in cohorts of hundreds of adults with RA, in whom the rate of severe adverse events was similar to that in patients receiving placebo (8) and lower than that in patients treated with methotrexate (15,30). Furthermore, the frequency of adverse events did not increase over time (8).

The first trial of etanercept in children with JRA involved 69 patients, only 2 of whom experienced severe adverse effects (9). The discrepancy between the results from that study and the findings in the current study cannot be explained by differences in the selection of the patients. The main baseline characteristics were similar in both studies, both of which included severely affected and heavily pretreated patients. One major difference, however, was that methotrexate was stopped in all of the patients in the other study but was maintained or restarted in 14 of our 61 patients. Nevertheless, all but 1 of the severe adverse effects reported in the present series occurred in patients who were not receiving methotrexate. Moreover, the combination of etanercept and methotrexate was well tolerated in large series of adults (14,15) and in small series of children with chronic arthritis (16,17).

In the present study, the high rate of treatment efficacy after 3 months, which was in accordance with the results of the first trial of etanercept in JRA (9), was followed by sustained improvement at 1 year in only a minority of patients. In the first published study of etanercept therapy for JRA, the followup was shorter than that in our study, because half of the patients had stopped using etanercept after the third month in order to receive placebo, while the patients who continued receiving etanercept were analyzed at month 7. The fact that in an intent-to-treat analysis, a much smaller proportion of our patients had improved after 6, 9, or 12 months than after 3 months could be explained, in part, by treatment withdrawals for severe side effects and in part by relapses or losses of efficacy between the third and the twelfth months. However, the flares of JIA that occurred in one-third of the patients in whom etanercept treatment was discontinued because of intolerance or lack of efficacy indicate that etanercept had at least some effect in controlling disease activity in some of these patients.

Even though the administration of methotrexate in some patients could theoretically have increased the rate of treatment discontinuation, by interfering with tolerance or response to treatment, this probably did not happen. Indeed, 6 of 14 patients who continued or restarted methotrexate while receiving etanercept improved by 30% at 1 year, which was similar to the percentage of improvement in the whole population. We also showed that the decrease in corticosteroid dosages after the third month in the patients who had responded to etanercept may have contributed to disease flare or loss of treatment efficacy in only a small proportion of these patients.

One of our aims was to compare the efficacy of etanercept in the 3 JIA onset groups. Systemic-onset JIA clearly represents a distinct entity, whereas the classification of some patients in 1 of the 2 other groups might have been more arbitrary, the polyarticular-onset JIA group being the most heterogeneous. In previous pedi-

atric series, only small numbers of patients with systemic-onset JIA treated with etanercept were reported (9,16,17,31). In adults, systemic-onset arthritis is rare, but a recent report showed that 7 of 12 of these patients improved after 6 months of etanercept therapy (32).

In the present study, the higher rate of treatment failure in the group with systemic-onset JIA may indicate that these patients are less responsive to anti-TNFα therapy, in a manner similar to their relative resistance to treatment with methotrexate (5–7). However, patients with systemic-onset JIA tended to have more severe symptoms at the beginning of etanercept treatment compared with other patients with JIA. In addition, patients with systemic-onset JIA had been treated with corticosteroids more frequently, for longer periods of time, and at higher dosages. Thus, beginning etanercept treatment earlier in patients with systemic-onset JIA may be worthwhile. This is consistent with the observation that other immunosuppressive treatments, such as methotrexate, are more effective in patients with systemic-onset JIA when initiated early (33).

In patients with JIA who fail to respond to etanercept, increasing the dosage seems to be ineffective in most cases (34). Patients who do not improve significantly after 3 months are probable candidates for other treatments, because no significant or sustained improvement was observed when etanercept treatment was continued in such patients. Interestingly, however, anti-TNFα therapy slows joint damage in adults with RA, even in the absence of clinical improvement (15,35). Long-term studies should be performed in patients with JIA, to monitor the effects of treatment on joint damage, growth, functional ability, and psychosocial outcome.

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