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Etanercept in the Treatment of Adult Patients With Still's Disease

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Objective. **To evaluate the safety and efficacy of etanercept in the treatment of adult patients with Still's disease.**

Methods. **Twelve adult patients who met criteria for Still's disease and had active arthritis were enrolled in a 6-month open-label trial of etanercept given in biweekly doses of 25 mg. The mean disease duration at study entry was 10.7 years. All patients had been treated unsuccessfully with other disease-modifying antirheumatic drugs. Efficacy was evaluated according to American College of Rheumatology (ACR) improvement criteria, and adverse events were recorded.**

Results. **Ten patients successfully completed the study; 2 withdrew due to disease flare. In 4 patients, the dosage of etanercept was increased from 25 mg biweekly to 25 mg 3 times per week. Seven patients met ACR 20% response criteria. Of these 7 responders, 4 met ACR 50% response criteria and 2 met ACR 70% response criteria. Among the 3 patients with systemic features of Still's disease (fever and rash), improvement in these features was seen in 1; the arthritis did not improve in any of these 3 patients. Except in the 2 patients who withdrew due to disease flare (rash, fever, and arthritis), no other significant adverse events occurred.**

Conclusion. **In this initial study of etanercept therapy for Still's disease in the adult, this treatment resulted in improvement in the arthritis and was well tolerated. Additional trials should be performed to elucidate the effects of tumor necrosis factor inhibitors in Still's disease.**

Still's disease (systemic-onset juvenile rheumatoid arthritis) is a systemic rheumatic disease of childhood which may persist into adulthood or may occur de novo in the adult population (1,2). It is classically distinguished by high fevers, evanescent rash, pharyngitis, fatigue, and arthritis. Other clinical features may include lymphadenopathy, hepatosplenomegaly, weight loss, and pleuritis. The illness is typically associated with leukocytosis, anemia, thrombocytosis, and marked elevation in the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and/or serum ferritin level. Generally, rheumatoid factor and antinuclear antibodies are negative.

Arthritis can occur in nearly 90% of patients with Still's disease. The pattern of joint involvement frequently includes the root joints such as hips, with larger joints often affected rather than smaller joints, and commonly with associated carpal or carpometacarpal ankylosis (3). Up to 50% of patients may develop a progressive and destructive polyarthritis (3–5). Prognosis depends on the pattern of disease expression and genetic factors. In many patients, the arthritis is refractory to standard therapies, including methotrexate (MTX). Currently used antirheumatic drugs have not been shown to produce substantial improvement in the various outcome measures that have been studied, including joint destruction, functional capacity, sustained gainful employment, and early mortality (4–7).

Blockade of tumor necrosis factor (TNF) has been used effectively in the treatment of a number of inflammatory arthritides, including rheumatoid arthritis

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(RA) and juvenile rheumatoid arthritis (JRA). TNFα is a proinflammatory cytokine that is released by activated macrophages and T cells and mediates a range of biologic and proinflammatory effects. Studies have demonstrated that TNFα is expressed at the cartilage–pannus junction, and increased TNFα concentrations are seen in synovial fluid of patients with active adult RA and JRA (8,9). Grom et al detected both TNFα and lymphotoxin (TNFβ) in the majority of synovial tissues obtained from patients with juvenile inflammatory arthritis (8). This is in contrast to findings in the synovial tissue of RA patients, in which lymphotoxin was not detected (9).

There has been limited experience with TNF blockade in Still's disease. Elliott et al (10) described a 16-year-old female patient with systemic-onset juvenile chronic arthritis who received 10 mg/kg of the monoclonal anti-TNFα (cA2; infliximab) and had a rapid resolution of fever and improvement in well-being; however, there was no change in the joint count or other clinical measures in this patient. A recent study of the use of a TNF blocking agent, etanercept, in patients with JRA demonstrated a positive clinical response in 74% of children receiving this treatment (11). Most of the children in that study had moderate-to-severe active polyarticular JRA; a subset were patients who had systemic disease that was refractory to MTX, or they could not tolerate MTX.

TNFα and lymphotoxin may be important in the pathogenesis of Still's disease. Therefore, we designed a pilot study, described herein, to evaluate the safety and potential efficacy of etanercept (which binds both TNFα and lymphotoxin) in adult patients who met criteria for Still's disease.

PATIENTS AND METHODS

Patient selection. This was an investigator-initiated Investigational New Drug study filed with the US Food and Drug Administration (no. 7783). Patients were recruited from 2 academic medical centers: the Brigham and Women's Hospital in Boston and Minor and James Medical Center in Seattle. The institutional review boards of both institutions approved the study. The study population consisted of adult patients who fulfilled the American College of Rheumatology (ACR) criteria for systemic-onset JRA (12). Although patients had to be at least 18 years of age to enroll in the study, the disease may have begun in childhood. Patients had to have active arthritis upon enrollment (defined as >8 swollen joints and >10 tender/painful joints, and at least 1 of the following: Westergren ESR >28 mm/hour, CRP >2.0 mg/dl, or duration of morning stiffness >45 minutes). All patients had to have previously been treated unsuccessfully with at least 1 disease-modifying antirheumatic drug (DMARD).

Patients were allowed to continue MTX (at a maximum dosage of 25 mg/week) and/or prednisone (maximum dosage of 20 mg/day) during the trial. The dosage of MTX was kept stable for at least 4 weeks and that of prednisone for at least 2 weeks prior to trial entry. No changes in dosage or medication were permitted during the study except in patients receiving prednisone at a dosage of >10 mg/day. Because of the concerns about the safety of prednisone given at these levels, the dosage could be decreased at the discretion of the investigator once the patient met criteria for response. The use of stable doses of nonsteroidal antiinflammatory drugs (NSAIDs) and analgesics was allowed throughout the study. Intraarticular and soft tissue corticosteroid injections were not allowed during the study. Patients who had significant concurrent medical diseases had previously used TNF blocking agents including etanercept or infliximab, or were pregnant or lactating were excluded.

Treatment protocol. This was a 6-month open-label pilot study. Etanercept, a recombinant form of the human 75-kd TNF receptor fusion protein, was administered subcutaneously at 25 mg twice weekly. No dosage reductions of etanercept were permitted in the first 8 weeks. If there was no clinical response (according to the ACR 20% response criteria for improvement in RA [ACR20] [13]) by 8 weeks, the dosage was increased to 25 mg 3 times per week.

Assessment. Clinical improvement in disease activity was defined according to the ACR20, at 6 months. After initial screening and baseline visits, the patients were assessed for response to etanercept at weeks 4, 8, 12, and 24 of the trial. Routine laboratory indicators of disease activity included hematology profile (months 1 and 3 only, and at month 2 for patients in whom dosing was increased to 3 times per week), chemistry profile, ferritin level, ESR, and CRP level. All patients had a followup evaluation 30 days after the last dose of study drug. All patients who received at least 1 dose of study drug were evaluated for adverse effects.

Statistical analysis. Calculations of ACR response were done on all patients. Patients who withdrew from the study were considered to be nonresponders irrespective of clinical response. For analysis of tender joints, swollen joints, and ESR, an intent-to-treat analysis taking into account early withdrawals was performed. Data were expressed as the mean $\pm$ SD where indicated. Differences in parameters before and after treatment with etanercept were examined for statistical significance using paired *t*-tests. *P* values less than 0.05 were considered significant.

RESULTS

Twelve patients with systemic-onset JRA were enrolled in the study. Eight patients were enrolled from Brigham and Women's Hospital and 4 from Minor and James Medical Center. The clinical characteristics of the patients at study entry are shown in Table 1. All patients met criteria for Still's disease as described above, and all patients had chronic polyarticular arthritis. In addition to the polyarthritis, 3 of the 12 had active systemic

Table 1. Baseline characteristics of the Still's disease patients and ACR response after 6 months of etanercept treatment*

Patient	Age/sex	Disease duration, years	No. of prior DMARDs	Tender/swollen joint count	ESR, mm/hour	Concomitant therapy	ACR response, %
1	34/F	17	4	28/23	42	MTX, pred.	70
2	36/M	8	4	22/14	19	MTX, pred.	NR
3	32/F	5	3	11/12	37	MTX, pred.	70
4†	42/M	2	1	17/8	29	Pred.	NR
5	19/F	12	2	25/18	4	NSAIDs alone	50
6	62/F	17	6	31/20	50	Pred.	NR
7	39/F	34	2	35/27	29	MTX	50
8	34/F	2	1	14/12	73	Pred.	50
9	39/F	3	3	48/44	135	MTX, pred.	20
10†	30/F	20	2	24/21	95	NSAIDs alone	NR
11†	33/F	9	2	12/10	39	Pred.	NR
12	30/F	1	1	18/14	84	Pred.	50

*ACR response = American College of Rheumatology criteria for improvement in rheumatoid arthritis (13,14); DMARDs = disease-modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; MTX = methotrexate; pred. = prednisone; NR = nonresponder; NSAIDs = nonsteroidal antiinflammatory drugs.
†Patient had systemic features including fever and rash.

features, including fever and rash, during the study. The cohort consisted of 10 women and 2 men. The mean age was 36 years (range 19–62), mean disease duration was 10.8 years (range 1–34), and mean age at onset of disease was 24 years (range 5–45). The average number of prior DMARDs used was 2.5 (range 1–6). Five patients had received MTX treatment in the past, and another 5 took MTX (mean 155 mg/week) during the study period. Nine patients were receiving prednisone at a mean dosage of 11.3 mg/day (range 5–20). At baseline, the mean ± SD number of swollen joints was 19 ± 10 and the mean ± SD number of tender joints was 24 ± 11. The mean ± SD ESR at entry was 52 ± 38 mm/hour. Four of 12 patients had childhood onset of disease (<18 years of age) which persisted into adulthood.

Ten patients successfully completed the study. Two withdrew due to disease flare (including rash, fever, and arthritis), at week 7 and week 13, respectively. Clinical response as defined by the ACR20 was observed in 7 patients. Of these 7 responders, 4 met ACR 50% and 2 met ACR 70% response criteria (14). In 4 patients, the dosage of etanercept was increased from 25 mg twice weekly to 25 mg 3 times per week without any adverse events. Of these 4 patients, clinical response occurred in only 1. The etanercept dosage was not decreased in any patient during the study.

At 6 months, there was a 67% improvement in the number of tender joints, a 63% improvement in the number of swollen joints, and a 27% improvement in the ESR. The mean ± SD number of tender joints at baseline decreased to 8 ± 9.8 ($P = 0.002$), the mean number of swollen joints decreased to 7 ± 5.8 ($P = 0.008$), and the ESR decreased to 38 ± 33 mm/hour ($P = 0.14$).

Of the 3 patients who had systemic features of Still's disease including fever and rash, only 1 reported improvement in these symptoms (but without concomitant improvement in the arthritis). The other patients with systemic features were the 2 who withdrew from the study due to disease flare as noted above.

Minor adverse events included injection-site reactions (3 patients), upper respiratory tract illness (3 patients), rash including Still's rash (3 patients), diarrhea (1 patient), and sinusitis (1 patient). No serious adverse events occurred during the study. Patients who received etanercept 3 times per week did not have an increased frequency of adverse events compared with those receiving the twice-weekly dosage.

DISCUSSION

In 1971, Bywaters described a series of 14 adult patients with arthritis and systemic features who did not appear to have classic RA and instead had symptoms identical to those found in the systemic form of JRA (1). Bujak et al described 10 similar cases observed in an 11-year period (15). This disease entity has now been coined adult-onset Still's disease, a well-recognized, distinct clinical rheumatologic entity. There is no pathognomonic finding in Still's disease; the diagnosis is

primarily one of exclusion. The pathogenesis of this disease remains unclear, and therapeutic targets for both the articular and the systemic symptoms have been poorly defined.

First-line treatment for Still's disease includes NSAIDs; however, their efficacy in controlling symptoms has been limited. Corticosteroid therapy is often necessary in order for clinical response to be achieved (7). Overall, the prognosis of Still's disease is good, but long-term steroid therapy is often needed to control symptoms, and up to 36% of patients have a chronic, polycyclic course (7). Many alternative medications have been tried in order to spare the effects of long-term corticosteroids. These medications, which include MTX, thalidomide, intravenous immunoglobulin, and azathioprine, have had variable effects on signs and symptoms of Still's disease.

The basis of using a TNF blocking agent in Still's disease stems from our understanding of the role of this cytokine in the pathogenesis of RA. TNFα is associated with tissue destruction in the joints of adult patients with RA (16). Previous clinical trials with anti-TNF agents in RA have demonstrated improvement in clinical and radiographic findings (17–19). In a study of 28 patients with JRA, Grom et al demonstrated that the pattern of TNFα expression was similar to that seen in adult RA (8). Furthermore, those investigators studied both TNFα and lymphotoxin expression in the synovium of JRA patients and compared the results with findings in adults with RA. Their study showed that although TNFα was the predominant cytokine in the synovium of both JRA and adult RA patients, lymphotoxin was also present in the synovium of JRA patients, in contrast to that from patients with adult RA. In addition, there were quantitative differences in the amount of TNFα and lymphotoxin among the subsets of JRA, with particularly increased expression of lymphotoxin in polyarticular JRA and juvenile spondylarthropathy. Thus, the predominance of lymphotoxin in polyarticular JRA and juvenile spondylarthropathy in contrast to pauciarticular JRA and adult RA may be a distinguishing feature among these inflammatory arthritides (8,9).

Other cytokines, including interleukin-6 (IL-6) and IL-18, have now been implicated in the pathogenesis of juvenile and adult-onset Still's disease (20–22). Studies related to the pathogenesis of systemic JRA have demonstrated markedly elevated levels of IL-6 in peripheral blood and synovial fluid of patients with active systemic JRA. These levels are significantly higher than those found in patients with other JRA onset types or adult RA (20,21). Furthermore, in the acute phase of systemic JRA, specifically in the presence of a characteristic high fever or rash, IL-6 levels corresponded with the fever curve (20). Another study demonstrated elevated levels of IL-18 in sera of patients with active Still's disease compared with other systemic rheumatic diseases such as RA and systemic lupus erythematosus (22). The IL-18 levels were found to correlate with serum ferritin values and disease severity in Still's disease patients.

There have been a limited number of preliminary studies, published in abstract form, on anti-TNF therapy in Still's disease, as well as 1 randomized withdrawal trial of etanercept in the treatment of JRA. The 2-part randomized withdrawal trial demonstrated efficacy of etanercept in polyarticular JRA (11). In the first part of this study (open label), 69 children with active polyarticular JRA received etanercept for 90 days. Twenty-two of the patients (32%) had systemic JRA. The second part of the study was a placebo-controlled withdrawal study in which the 51 children (74%) with a clinical response (from the first part of the study) were randomized to continue etanercept or receive placebo for 4 additional months. Of the children whose disease responded, 24% of those who continued to receive etanercept experienced disease flare, as compared with 77% of the children who were receiving placebo. In this second part, 17 of the children who had systemic-onset JRA continued in the trial (8 receiving placebo and 9 receiving etanercept). Forty-four percent of the systemic-onset JRA patients receiving etanercept experienced disease flare, as compared with 88% of those receiving placebo.

In addition to the above-mentioned report on 1 child who received infliximab with improvement in systemic features of Still's disease but without improvement in joint disease (10), there have been several abstracts on etanercept and infliximab in JRA patients; these studies have included some patients with Still's disease (23–26). In general, these abstracts reported a clinical response to inhibitors of TNF in patients with Still's disease (23–26). One abstract described a survey of 122 pediatric rheumatologists, which showed that 42% of children had at least a 60% response to etanercept and 33% had little or no response to therapy (23). In a subgroup with systemic features of JRA, 64% responded to etanercept. In comparison with other types of JRA, however, patients with systemic features of JRA did not show as great a response to etanercept.

In another study, 9 children with active systemic JRA were treated with etanercept (starting at 0.4 mg/kg subcutaneously twice per week) and had a variable

response (24). Four of the 9 patients had an excellent initial clinical response within 2 months, and 4 had little or no benefit from etanercept. Unfortunately, all 4 patients who were responders developed a major exacerbation within 6 months of starting etanercept, and these flares were temporally related to reduction in the dosage of concomitant MTX or prednisone. Those with systemic JRA were less likely to have an impressive response to etanercept and more likely to experience a flare of disease after initial improvement, as compared with the polyarticular JRA patients.

Another abstract described 5 patients with recalcitrant adult-onset Still's disease, all of whom exhibited significant improvement after 3 weeks of etanercept therapy (25). Four patients completed 6–12 months of etanercept treatment and remained in clinical remission while also receiving lower doses of prednisone (7.5–10 mg). In an open trial in 10 children with severe active refractory juvenile chronic arthritis, including 1 with active Still's disease, very good response was achieved in all patients after the second infusion of infliximab (26).

The results of the present open-label trial demonstrate the potential benefit of etanercept in the treatment of Still's disease with active arthritis. Although this was a pilot study without a control group or randomization, a high percentage of patients (66.7%) had improvement in their arthritis after etanercept therapy was instituted. Of the 3 patients with systemic features, these symptoms improved during etanercept treatment in only 1. The side effects observed in this small trial were limited to minor adverse events, including upper respiratory tract infections, injection-site reaction, and 1 case of sinusitis. There were no deaths or major adverse events during the study. Given the limited number of treatment options in Still's disease and the potential of TNF blockade to be of benefit in this disorder, multicenter randomized controlled trials should be performed to further define the role of TNF blockade in Still's disease.

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