

Efficacy of Etanercept in Preventing Relapse of Uveitis Controlled by Methotrexate

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Objective: To evaluate the efficacy of etanercept vs placebo in preventing relapses of uveitis in patients taking methotrexate with control of uveitis and whose methotrexate dosage was being tapered.

Methods: Patients with chronic or recurrent noninfectious uveitis with inflammation controlled by low-dose methotrexate were randomized to either the drug or placebo group in a double-masked manner, given a methotrexate taper schedule, and followed for 24 weeks. The main outcome measures were control of inflammation, visual acuity, and adverse reactions. Data were analyzed both as an attempt-to-treat analysis and an analysis only of those patients who completed the study.

Results: A total of 20 patients were randomized to the drug and placebo groups. Relapse of uveitis occurred in 3 of 10 patients in the treatment group and 5 of 10 patients in the control group. Two patients in the treatment group withdrew prematurely from the study due to adverse effects. There was no significant difference between the treatment and placebo groups with regard to the rate of relapse and the final visual acuity. No patient suffered from any irreversible, long-term morbidity or mortality.

Conclusion: Etanercept has no significant efficacy over placebo in preventing relapses of uveitis in patients being tapered from methotrexate.

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TUMOR NECROSIS factor α (TNF- α) is an inflammatory mediator produced by macrophages and activated T cells that is important in the pathogenesis of several immune-mediated disorders, including rheumatoid arthritis.^{1,2} The natural inhibitor of TNF- α in vivo is a soluble form of the TNF- α receptor (TNFR). In vivo, there are 2 subtypes of this receptor, p55 and p75, both of which have an equal affinity for TNF- α and equivalent inhibiting actions. These inhibitors bind TNF- α in the serum, preventing it from binding TNFR on the surface of cells and therefore antagonizing its action.¹ Antibodies to TNF and a recombinant TNFR can inhibit the action of TNF in vivo. Phase II and III clinical trials using recombinant soluble TNFR for the treatment of patients with rheumatoid arthritis have demonstrated the efficacy of this drug in improving the inflammatory symptoms associated with rheumatoid arthritis, with minimal adverse effects.³⁻⁵ An animal study of experimental autoimmune uveitis has shown a marked decrease in tissue destruction following in-

hibition of TNF- α activity,⁶ and one study of TNF- α in humans with uveitis showed increased TNF- α levels in 26% of the vitreous specimens investigated (it should be noted, however, that most patients with uveitis in this report were being operated on because of retinal detachment or proliferative diabetic retinopathy).⁷ These observations naturally stimulated interest in the idea that TNF- α inhibition might be therapeutic for patients with uveitis, and uncontrolled studies in small numbers of patients yielded promising results.⁸

Methotrexate has been widely used in the treatment of ocular inflammatory disorders, particularly uveitis. Although well tolerated by patients, methotrexate has potential adverse effects, which can limit its use in some patients. We therefore investigated (in a randomized, double-masked, placebo-controlled clinical trial) whether TNF- α inhibition by etanercept could prevent relapse of uveitis in patients with a history of previously recurrent, steroid-dependent uveitis that had been successfully treated (ie, no recurrences and not taking any steroids) with methotrexate as methotrexate was tapered and discontinued.

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Etanercept is a recombinant human TNFR p75-Fc fusion protein. It is administered as a subcutaneous injection twice a week, with a maximum dose of 16 mg/m². The most common adverse effects are mild injection site reaction (erythema or erythema plus discomfort), which did not cause discontinuation of the drug in any patient in the phase I trial⁵ and caused discontinuation of the drug in 1 patient (of 136 patients taking etanercept) in the phase II clinical trial.⁴ Transient mild upper respiratory tract symptoms (cough, rhinitis, sinusitis, upper respiratory tract infection, and pharyngitis) were noted and resolved without interruption of the etanercept dosing and occurred most frequently in the 2 mg/m² and 16 mg/m² groups.⁴ Other nonrespiratory infections were rare and never serious. However, etanercept significantly increased mortality when administered to patients with gram-negative sepsis and hypotension. It has also been shown to cause intestinal obstruction in patients with Crohn disease. No major abnormalities in the hematologic and serum chemistry profiles have been noted in patients treated with etanercept.⁴

No neutralizing antibodies to this drug have been detected by enzyme-linked immunosorbent assay during or after treatment in the published clinical trials. The long-term effects of etanercept treatment on serious infection, malignancy, and autoimmune disease are unknown.

METHODS

The protocol was reviewed and approved by the institutional review board of the Massachusetts Eye and Ear Infirmary, Boston. All patients 18 years or older being treated at the Massachusetts Eye and Ear Infirmary Immunology and Uveitis Service for recurrent uveitis and taking a low dosage (≤ 0.15 mg/kg per week) of methotrexate for at least 12 weeks with control of uveitis (not taking a topical steroid) were offered inclusion in the study. Methotrexate was the only systemic immunomodulatory drug used in these patients within a period of 4 weeks before the start of the study. Steroid eyedrops were administered only to treat acute episodes of uveitis following patients' enrollment in the study, and these were then tapered and discontinued after achieving control of inflammation. Pregnant patients, patients known to have hypersensitivity to etanercept or any of its components, and those with Crohn disease, sepsis, active infection at the time of enrollment, or uncontrolled diabetes mellitus were excluded from the study.

Informed consent was obtained on enrollment of the patient in the study, and patients were screened to ascertain if they met all the enrollment criteria. Patients were then randomized to 1 of the 2 groups, the treatment (etanercept) group and the control group. The required examination and investigations were then conducted, and the patient was given the masked medication or placebo by an investigator and instructed in the method of its use. The test article (etanercept) and the control article (isotonic sodium chloride solution) were both administered subcutaneously. The dosage of the study medication was 25 mg, and it was administered subcutaneously, twice a week, starting on day 0 of the study and continuing throughout the study period. Study medications were masked by Immunex Corporation, Seattle, Wash, and then sent to the Massachusetts Eye and Ear Infirmary pharmacy.

On the initial visit, general information regarding history (demographic characteristics, medication, and medical history) was recorded. Both eyes underwent an external examination, visual acuity measurement, slitlamp biomicroscopy, pressure measurement, and a dilated fundus examination. Additional laboratory tests were ordered, including a complete blood cell

count, alanine transaminase, aspartate transaminase, alkaline phosphatase, serum urea nitrogen, and creatinine levels, a pregnancy test if applicable, and markers of inflammation, including erythrocyte sedimentation rate, C-reactive protein level, C3, C4, Raji cell assay, total complement levels, and TNF- α levels. Methotrexate was tapered at 2.5 mg/wk starting at 2 weeks after the first dose of study medication. The study medication was dispensed according to the randomization schedule, and its use was explained. The first injection was performed under the supervision of site personnel. Patients were then scheduled to return every 4 weeks for the total study period of 24 weeks. They were also instructed to return to the clinic at any time between the scheduled visits if they felt the need to do so.

At each follow-up visit, a complete history was recorded, and a complete examination was performed with specific inquiries regarding adverse effects of the medication, flare-ups of uveitis, and current dosage of methotrexate. Blood work (a complete blood cell count, liver function tests, and renal function tests) was performed. Additional studies to assess activity of the immune system (erythrocyte sedimentation rate, C-reactive protein level, C3, C4, Raji cell assay, total complement levels, and TNF- α levels) were performed at 2 different points during the course of the study.

Patients were excluded from the study if at any time during the investigation they needed any medication other than topical steroids or cycloplegics for ocular symptoms related to uveitis. The study medication was discontinued if at any point during the study the patient did not wish to continue participating owing to an adverse event or the investigator considered it inadvisable for the patient to continue in the study. If the patient developed an infection requiring treatment with antibiotics, the study medication was discontinued until the infection was treated and controlled. Appropriate therapy was instituted, and the patient was followed until resolution of symptoms. Unexpected complaints and complications were recorded as adverse events, and their onset, duration, severity, and possible relationship to the treatment were also recorded. The exceptions were mild flulike symptoms, and mild erythema and reaction at the injection site, which were not recorded as adverse reactions. Patients were also discontinued from the study if they were noncompliant with the study regimen, were lost to follow-up, or personally decided to discontinue the study.

The research followed all the tenets of the Declaration of Helsinki. If a serious adverse event occurred and it was necessary to identify the study treatment to ensure the safety of the patient, the treatment code was broken. All patients receiving the drug were evaluated for safety and intent-to-treat analysis. All patients receiving etanercept, meeting inclusion and exclusion criteria, and having at least 2 follow-up visits were included in the efficacy analysis. The statistical objective of this study was to demonstrate the efficacy of etanercept over placebo in preventing flare-ups of recurrent uveitis in patients being tapered from methotrexate. The primary outcome parameters were presence or absence of flare-ups and the number of flare-ups during the study period. A successful outcome was defined as a complete absence of flare-ups during the study period.

The data were analyzed at the end of the study using Microsoft (Redmond, Wash) Excel 2000 software. The Fisher exact test was the statistical instrument employed for the assessment of significance of differences observed in recurrences, and $P < .05$ was considered significant.

RESULTS

Twenty patients with previously recurrent or chronic uveitis controlled with low-dosage once-weekly methotrex-

ate but being tapered from methotrexate treatment were treated (10 with etanercept and 10 with the placebo) for a period of 24 weeks. The mean age of onset of uveitis was 48 years in patients being treated with etanercept and 45 years in patients being treated with the placebo. Seven women were taking etanercept, and 9 women were taking the placebo.

The mean dosage of methotrexate, at the time of initiation of the study medications, was 15 mg/wk for patients taking etanercept and 12 mg/wk for patients receiving the placebo. Patients taking etanercept had been treated with methotrexate for a mean duration of 25 weeks, whereas those taking the placebo had received methotrexate treatment for a mean duration of 21 weeks.

The various categories of uveitis are presented in the **Table**. Idiopathic uveitis was the largest category in both treatment groups. This was followed by HLA-B27, systemic lupus erythematosus, and rheumatoid arthritis, in patients being treated with etanercept. The other causes of uveitis in patients receiving the placebo medication were HLA-B27, systemic lupus erythematosus, juvenile rheumatoid arthritis, and idiopathic. The χ^2 testing did not reveal any significant difference in control of inflammation with regard to age, sex, the dosage or duration of methotrexate treatment, or the underlying etiology of uveitis in either of the study groups.

From the total population of patients receiving etanercept, 5 patients (10 eyes) experienced sustained remission of uveitis without relapses, 3 patients (6 eyes) had relapse of uveitis, and 2 patients withdrew from the study (Table). Five patients (10 eyes) receiving the placebo medication experienced no relapses of uveitis, and 5 patients (10 eyes) had a relapse of uveitis during the course of therapy with the placebo medication. There was no statistically significant difference between the 2 groups (etanercept vs placebo) in terms of relapses of inflammation experienced by the patients ($P = .66$; Fisher exact test) during the course of therapy.

In the etanercept treatment group, there was no change in visual acuity in 18 eyes (90%), whereas 2 eyes (10%) experienced a decrease in visual acuity of more than 2 lines (Table). One of the 2 eyes showing a decrease in visual acuity of more than 2 lines was measured at the exit visit from the study when the patient had an acute episode of uveitis; visual acuity returned to baseline after resolution of the acute episode. There was no change in visual acuity during the course of therapy in any of the 20 eyes of patients being treated with the placebo medication.

Adverse events prompting discontinuation of etanercept occurred in 2 patients (10%) (Table). One patient discontinued because of increased narcolepsy and cataplexy (which were preexistent), and another patient discontinued etanercept because of difficulty with injections. None of the patients receiving the placebo had to discontinue the medication owing to adverse reactions.

Gastrointestinal symptoms (nausea, diarrhea, upset stomach, and bleeding from the rectum) were experienced by 2 patients in each treatment group, whereas 1 patient in each group experienced headaches. One patient taking etanercept had a urinary tract infection, whereas another patient taking placebo experienced flu-

Demographic Characteristics and Main Outcome Measures in Patients Taking Etanercept or Placebo*

Parameter	Etanercept (n = 10)	Placebo (n = 10)
Demographic Characteristics		
Mean age, y	48	45
Female sex	7	9
Methotrexate dosage, mg/wk	15	12
Duration of methotrexate treatment, wk	25	21
Uveitis category		
Idiopathic	5	7
HLA-B27-associated	2	1
SLE-associated	2	1
Arthritis-associated	1 (RA)	1 (JIA)
Main Outcome Measures		
Uveitis relapse		
No relapse	5	5
Relapse	3	5
Withdrew from study	2	0
Visual acuity change, No. of eyes		
Increase >2 lines	0	0
No change	18	20
Decrease >2 lines	2†	0
Adverse events		
Urinary tract infection	1	0
Gastrointestinal symptoms (eg, nausea, diarrhea, upset stomach)	2	2
Increased narcolepsy and cataplexy	1 (Discontinued)	0
Headache	1	1
"Flu"	0	1
"Could not tolerate"	1 (Discontinued)	0

Abbreviations: JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

*Data are presented as the number of patients unless otherwise indicated.

†One of the 2 eyes showed a decrease of more than 2 lines measured at the exit visit when the patient had an acute episode of uveitis; visual acuity returned to the baseline level after resolution of the acute episode.

like symptoms. There was no long-term morbidity due to the medications.

COMMENT

Similarities between the immune mechanisms that cause autoimmune arthritis and uveitis have led to rheumatologists and ophthalmologists sharing many of the same drugs to treat arthritis and uveitis—steroids, nonsteroidal anti-inflammatory drugs, and immunomodulators, such as methotrexate, cyclosporine, and mycophenolate mofetil.⁹⁻¹¹ The dramatic efficacy of etanercept in treating rheumatoid arthritis raised hopes that this more focused, less potentially toxic systemic immunomodulatory medication might be effective in the treatment of patients with chronic, recurrent, or otherwise treatment-resistant, steroid-dependent uveitis.

Initial reports on the efficacy of etanercept for uveitis therapy have been varied. Smith et al¹² treated 9 patients with uveitis with etanercept or infliximab. Only 3 of those 9 cases of uveitis improved; the drugs appeared to be more effective in controlling the associated arthritis. Reiff et al⁸ treated 10 children (16 eyes) suffering from treatment-resistant uveitis with etanercept. Ten of the 16 eyes responded with some reduction in inflammation, and 4 showed complete remission of uveitis.

Four additional abstracts address the issue of anti-TNF- α therapy with infliximab (a monoclonal antibody that binds TNF- α) for uveitis. El-Shabrawi and Graz¹³ treated 7 patients with acute anterior uveitis; 3 patients responded with resolution of the uveitis. Banares et al¹⁴ treated 7 patients with posterior uveitis with etanercept; 5 patients reportedly showed improvement. Honkanen et al¹⁵ concluded that TNF- α inhibition might be beneficial in selected cases of juvenile idiopathic uveitis. However, until now, these case series have not been substantiated by a study that takes into account and controls for other factors, such as the natural history of the disease, placebo effect, and bias. Our randomized, double-masked, placebo-controlled study shows that there is no significant difference between patients treated with etanercept and those given placebo in terms of relapse rates of uveitis; etanercept is not superior to placebo in preventing relapse of uveitis. And although it is true that the power of this randomized controlled trial is limited because of the number of patients in it, the fact remains that any large effect from anti-TNF- α therapy would have been detected, and small effects probably do not warrant serious consideration of such therapy. Thus, methotrexate remains an important choice for recurrent or chronic uveitis.^{8,10-12}

The lack of significant benefit of etanercept therapy in preventing relapses of uveitis is disappointing, but it is frankly not surprising. Although TNF- α is clearly a critically important cytokine involved in synovial inflammation in patients with rheumatoid arthritis,^{12,16} our efforts to identify it in aqueous humor and in vitreous of patients with uveitis have failed (V. Perez, MD, G. Papaliodis, MD, D.C., and C.S.F., unpublished data).

We therefore believe that the cellular and cytokine molecular details of intraocular inflammation differ from those of rheumatoid arthritis. Although it may be that inhibition of a single cytokine (eg, interleukin 1 or interleukin 6) may help in the care of selected patients with uveitis, it may also be true that the inflammatory process in the eye is too complex to lend itself to such monotherapy.

Limitations of this study include the small sample size, which can detail only large differences in the relapse rates between methotrexate and etanercept. Studies with a larger sample size are needed to confirm these results and to detect relatively small changes in the relapse rate.

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