

Etanercept, a soluble tumor necrosis factor receptor, palliates constitutional symptoms in patients with myelofibrosis with myeloid metaplasia: results of a pilot study

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Patients with myelofibrosis with myeloid metaplasia (MMM) often experience debilitating constitutional symptoms such as drenching night sweats, profound fatigue, unexplained fevers, and unintentional weight loss. Tumor necrosis factor (TNF) contributes to organ fibrosis and hypercatabolic symptoms in a variety of disease states. We conducted an open-label pilot study of etanercept, a soluble

TNF receptor, administered at a dose of 25 mg subcutaneously twice weekly for up to 24 weeks in 22 patients with MMM. Of 20 evaluable patients, 12 (60%) experienced an improvement in constitutional symptoms, and 4 (20%) had an objective response (improvement in peripheral cytopenias or spleen size). The degree of marrow fibrosis was unchanged, and only minor changes in overall marrow cellular-

ity were observed. Toxicity was mild, with injection site reactions (20%) and minor infections (10%) as the most common side effects. One patient developed reversible pancytopenia. Etanercept may be useful for palliation of constitutional symptoms in MMM. (Blood. 2002;99:2252-2254)

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Introduction

Myelofibrosis with myeloid metaplasia (MMM) is an aggressive clonal myeloproliferative disorder characterized by peripheral blood cytopenias, reactive marrow fibrosis, and extramedullary hematopoiesis.¹ Constitutional symptoms such as night sweats, low-grade fevers, fatigue, and cachexia are common and debilitating in MMM, but currently available treatments for the disease have little effect on these symptoms.

Several cytokines are implicated in the pathogenesis of marrow fibrosis.² These cytokines include transforming growth factor β , basic fibroblast growth factor, vascular endothelial growth factor, platelet factor 4, calmodulin, and tumor necrosis factor (TNF).¹ TNF directly inhibits hematopoiesis,^{3,4} stimulates fibroblast proliferation,⁵ and is a key mediator of fever and cachexia.^{6,7} Anti-TNF approaches are currently being evaluated in cancer-related cachexia and in a wide range of disorders associated with fibrosis.

We hypothesized that anti-TNF therapy might be effective in MMM. We report an open-label pilot study of etanercept, a dimeric soluble recombinant form of the extracellular domain of human p75 TNF receptor fused to the Fc fragment of human immunoglobulin G1, in patients with MMM complicated by anemia and/or constitutional symptoms.

consent before study enrollment. To be eligible, patients had biopsy-confirmed MMM (a senior pathologist, C.-Y.L., reviewed all marrow samples) and did not have the *bcr-abl* translocation. We excluded patients with pre-existing infections or poor liver or kidney function (direct bilirubin level higher than 2 times the upper limit of normal, aspartate aminotransferase level higher than 5 times normal, or creatinine level higher than 2.0 mg/dL). All other therapies for MMM, including hematopoietic growth factor support, were stopped at least 4 weeks before trial initiation.

Intervention

The institutional review board of the Mayo Clinic approved the study protocol. Patients self-administered 25 mg etanercept (Enbrel; Immunex, Seattle, WA) subcutaneously twice weekly. Patients responding to therapy at 12 weeks had the option to continue the drug for an additional 12 weeks. All patients completing 24 weeks of therapy underwent a follow-up marrow biopsy.

Outcome assessment

There are no standard response criteria for clinical trials in MMM. The minimal responses we defined as necessary to qualify as a clinically meaningful improvement in this trial are listed in Table 1.

At the start of the trial and every 4 weeks thereafter, we asked patients about the following symptoms: presence or absence and degree of night sweats and fevers, daily mean fatigue level using a 10-point numerical analog scale, and unintentional weight loss. We weighed patients at enrollment and monthly thereafter. Spleen size was determined by physical examination.

Study design

Study participants

We recruited patients with MMM from the hematology practice at the Mayo Clinic in Rochester, MN. All patients gave informed

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Submitted August 30, 2001; accepted October 31, 2001.

Presented at the 43rd annual American Society of Hematology meeting, Orlando, Florida, December 2001.

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Table 1. Minimal responses necessary to qualify as a clinically relevant improvement

Characteristic	Minimal response
Hemoglobin level	Stable increase by 1 g/dL or > 50% decrement in transfusion requirements
Platelet count	More than 50% increase and minimum absolute increase of 20 000/mm ³
Spleen size	More than 50% reduction and over 2 cm absolute reduction in linear dimension of spleen palpable below the left costal margin
Weight loss	Cessation of weight loss
Night sweats	Improvement in frequency and intensity of drenching night sweats by more than 75%
Fatigue	2-point or greater improvement in mean self-reported daily fatigue level (on a modified 10-point numerical analog scale) and statement that the patient felt this improvement was meaningful
Fever	Resolution of fevers

All responses had to continue for at least 4 weeks.

Results and discussion

We enrolled 22 patients in this study. Of these, 2 patients were excluded shortly after enrollment: one patient with a pre-existing but undiagnosed dental abscess, and a second patient traveling to Mexico who forgot to take the study medication with him. These

patients took less than 2 weeks of study medication. Of the 20 evaluable patients (aged 45-82, 15 men), 18 had anemia, 8 had thrombocytopenia, and 13 had palpable splenomegaly at the time of trial enrollment (3 had previously undergone splenectomy) (Table 2). With regard to constitutional symptoms, 8 patients had drenching night sweats, 7 complained of unintentional weight loss in the previous 6 months (ranging from 5 to 23 kg, median of 7 kg), 1 had persistent unexplained low-grade fevers, and all 20 patients complained of excessive fatigue.

Objective responses were seen in 4 patients (Table 2). There were 3 hemoglobin responses (1 increase in hemoglobin by 3 g/dL and achievement of transfusion independence, 1 stable increase in hemoglobin by 1 g/dL, and 1 decrease in red cell transfusion requirements by > 50%), 1 platelet response (increase from 16 000 to 182 000/ μ L), and 1 spleen response (decrease from 10 cm to 2 cm below the costal margin on shallow inspiration). However, 1 patient had marked worsening in his blood counts (hemoglobin dropped from 8.2 g/dL to 6.3 g/dL, absolute neutrophil count from 2630 to 640/ μ L, and platelet count from 166 000 to 136 000/ μ L). This patient was the only person who discontinued the drug because of toxicity, and the cytopenias resolved promptly.

Overall, a constitutional improvement of one type or another was seen in 12 of 20 patients. Improvements were seen in 6 (75%) of 8 patients with drenching night sweats (5 of the 6 enjoyed complete cessation), 7 (100%) of 7 patients with unintentional weight loss (2 simply stopped losing weight and 5 gained weight

Table 2. Clinical data for evaluable patients receiving etanercept

Patient no.	Hemoglobin level before Rx (g/dL)	Hemoglobin level after Rx (g/dL)	Receiving transfusion support? If so, how often? Any change during the trial?*	ANC before Rx ($\times 10^9/L$)	ANC after Rx ($\times 10^9/L$)	Platelet count before Rx ($\times 10^9/L$)	Platelet count after Rx ($\times 10^9/L$)	Spleen size before Rx† (cm)	Spleen size after Rx† (cm)	Weight loss‡ (kg)	Weight change§ (kg)
1	14.2	16	No	8.7	13.1	161	98	18	15	Y/6	Gain/2.7
2	8.6	9.1	Yes/q2wk/NC	0.7	0.6	69	60	20	20	N	Stable
3 ¶#	7.7	8.2	Yes/q1mo/NC	2.7	2.4	600	451	S	S	Y/5	Stable
4	9.6	9.0	Yes/q1mo/NC	1.7	1.4	45	39	0	0	N	Gain/4.5
5¶	7.1	8.0	Yes/q5wk/NC	3.0	1.8	577	460	S	S	N	Stable
6	11.4	9.2	Yes/q2wk/NC	70.6	68.9	47	54	S	S	N	Stable
7 #	10.3	9.5	No	5.9	3.9	164	122	5	5	Y/5	Gain/5
8	9.9	10.2	No	12.5	9.6	246	365	4	4	N	Stable
9 ###	8.2**	11.3**	Yes/q8wk/∅**	40	59.8	16**	182**	20	20	Y/23	Gain/2.3
10	8.2	6.3	No/q1wk	2.6	0.6	166	136	8	14	N	Stable
11 #	12.5	11.4	No	13.6	11.1	190	166	9	10	Y/9	Gain/2.7
12#	10.0	9.2	Yes/q5mo/q1wk	8.8	15.7	58	78	20	17	N	Stable
13	9.7	9.4	No	2.7	3.2	224	268	7	7	N	Gain/3.2
14#	10.3	11.5	Yes/q2wk/NC	10.5	5.9	31	32	0	< 1	N	Gain/1.8
15#**	9.4**	10.7**	No	6.6	4.6	192	173	0	0	N	Stable
16 ¶###	10.0**	12.0**	Yes/q1wk/q7wk**	4.1	2.6	162	129	0	0	Y/14	Stable
17 ¶###	11.9	12.4	No	7.8	8.6	100	86	10**	2**	Y/7	Gain/1.2
18	9.7	10.0	No	2.8	3.7	257	223	5	5	N	Stable
19¶#	7.5	7.1	Yes/q1mo/NC	5.8	7.1	79	86	19	18	N	Gain/1.5
20	9.6	8.2	No	18.1	22.2	390	382	28	30	N	Stable

Rx indicates therapy with etanercept; ANC, absolute neutrophil count.

*For patients who were receiving transfusion support, the average frequency of transfusion during the 6 months before trial enrollment is listed (transfusion threshold of approximately 8.0 g/dL was used for patients without cardiovascular disease), followed by the frequency of transfusion requirement during the trial. NC indicates there was no change in the frequency of transfusion requirement during the trial. ∅ identifies the patient who achieved transfusion independence during the trial. Patient 10 became transfusion dependent during the trial, and the study medication was discontinued because of pancytopenia.

†S indicates patients who had undergone a splenectomy before trial enrollment. All measurements for spleen size are centimeters below the left costal margin on shallow inspiration.

‡Self-reported unintentional weight loss in the 6 months before trial enrollment.

§Measured weight change during therapy with etanercept. Patients who gained weight but had not described problematic cachexia are not included as responders.

||Experienced complete gain.

¶Experienced complete cessation of night sweats. Patient 11 had a more than 75% reduction in night sweats. Patients 1 and 6 had night sweats, but there was no response to etanercept therapy. Patient 13 actually developed night sweats while enrolled in the trial.

#Experienced an improvement in their level of fatigue and general performance status during the trial. All patients complained of fatigue at trial enrollment.

**Considered to have at least a partial hemoglobin or platelet count or spleen size response (details in text).

with range from 1.2 to 5 kg), and 10 (50%) of 20 patients with fatigue. Four patients who did not complain of weight loss at the beginning of the trial gained weight during the study (range, 1.5-4.5 kg). We observed no improvement in the 1 patient with unexplained fevers.

In addition to the 1 patient with pancytopenia, toxicity attributable to the drug included mild injection-site reactions in 4 patients, development of new low-titer antinuclear antibody in 2 patients, minor infections (upper respiratory infections and gastroenteritis) in 2 patients, and myalgias, abdominal cramping, and mild sedation on the day of injection in 1 patient each. No serious infections were observed. One patient who did not have night sweats at the beginning of the study developed them while on the study.

Nine responding patients elected to continue therapy for the full 24 weeks and underwent a follow-up marrow biopsy. There were no changes in the degree of marrow fibrosis. Minor alterations in overall marrow cellularity were seen, but these alterations were not consistent and sampling error cannot be excluded.

In this preliminary study, etanercept at a dose of 25 mg subcutaneously twice weekly was well tolerated and relieved troubling constitutional symptoms in some patients with MMM. We observed several objective and clinically significant responses in peripheral blood counts and spleen size, but caution is warranted because one patient developed pancytopenia. We did not observe a change in marrow fibrosis in this study. This finding may be because etanercept has no effect on marrow fibrosis or because 24 weeks of anti-TNF therapy may not be long enough to effect a change in marrow fibrosis.

This study is limited by its relatively small sample size (in part due to the rarity of MMM), the subjective nature of constitutional

end points, and the lack of blinding of patients and outcome assessors. Therefore, these results will need to be confirmed in a larger, randomized study using placebo or active controls and with appropriate blinding of patients and outcome assessors. In light of these preliminary results, similar studies of the palliative role of other anti-TNF agents (eg, infliximab) should be conducted.

If more definitive studies confirm this study's promising results, the widespread use of etanercept in MMM may be limited by the need for parenteral administration and by its high cost. The wholesale pharmacy cost of 8 doses (25 mg) of etanercept in our institution is US\$888, and facility and administration charges increase the patient price to more than US\$1600 per month. In fact, several patients in this trial who wanted to continue etanercept beyond the completion of this study could not pay for the drug and had to discontinue it. A financial assistance program is available from the manufacturer.

In conclusion, etanercept may be safe and effective in palliating constitutional symptoms in some patients with MMM. The most severe toxicity observed was reversible pancytopenia. Patients with MMM and bothersome hypercatabolic symptoms may benefit from a trial of this medication.

Acknowledgments

Etanercept was provided free of charge to the patients for the duration of the study by the Immunex Corporation of Seattle, WA. The drug manufacturer did not have access to or control of study data and did not participate in the preparation of this report. We thank Dr Victor Montori for his helpful comments on the manuscript.

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