A Pilot Study of Etanercept Treatment for Pemphigus Vulgaris

Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease associated with a high morbidity rate and potential mortality. Current therapies are not uniformly effective and are associated with potential adverse effects; thus, there is a need for new therapeutic options for PV.

Data from in vitro experiments and mouse models suggest that tumor necrosis factor (TNF) has a role in PV pathogenesis. Etanercept is a recombinant fusion protein of the extracellular ligand-binding domain of human 75-kDa TNF receptor and the Fc portion of human IgG1 that acts as a competitive inhibitor of TNF. We conducted a pilot study to evaluate the efficacy and safety of etanercept for PV therapy.

Methods. This double-blinded, randomized, placebo-controlled trial was approved by the institutional review board. All patients were older than 18 years and had undergone a skin biopsy with findings consistent with PV on both routine histologic analysis and direct immunofluorescence microscopy. They had no alteration in systemic or topical immunomodulatory therapy for 4 weeks prior to enrollment.

Subjects were randomized at a ratio of 2:1 to receive etanercept (50 mg) or placebo (saline) subcutaneous (SC) injections once weekly for 16 weeks. The primary end point of the study was the mean time to achieve 50% reduction in the number of active lesions. Power analysis yielded a sample size of 13 to detect a difference of 35 days between placebo and etanercept therapy, assuming an SD of 30 days in both groups at $\alpha = .05$ and a power of 0.8.

Results. Owing to slow enrollment and a futility analysis suggesting that study completion would not change our conclusions, the trial was halted after enrollment of 8 participants. Two patients dropped out of the study (both in the etanercept group)—one at week 4 secondary to a PV flare and the other at week 8 secondary to a hip fracture. The primary end point of 50% reduction in lesion number was met by 3 of the 6 subjects completing the study (2 in the placebo group, 1 in the etanercept group) (Table). Of the 3 participants in the etanercept group for whom the treatment failed, 1 (patient 5) experienced clinical improvement and was able to taper

Table. Data Summary

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Disease</th>
<th>Concomitant Therapies at Baseline (Time Undergoing Therapy)</th>
<th>Study Group</th>
<th>Baseline/Week 16</th>
<th>Adverse Events/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study Lesions, No. DLQI PGA</td>
<td></td>
<td>Week 16</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration, y Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M/73</td>
<td>6</td>
<td>M Pred, 23 mg QOD (70 mo) MMF, 3250 mg/d (63 mo)</td>
<td>Etan</td>
<td>10/11b</td>
<td>1/1b</td>
</tr>
<tr>
<td>2/F/58</td>
<td>1</td>
<td>M Pred, 5 mg/d (14 mo) AZA, 150 mg/d (14 mo)</td>
<td>Plac</td>
<td>9/4</td>
<td>4/4</td>
</tr>
<tr>
<td>3/F/35</td>
<td>13</td>
<td>C Dexa swish twice daily (14 mo) AZA, 150 mg/d (18 mo)</td>
<td>Plac</td>
<td>54/13d</td>
<td>30/1d</td>
</tr>
<tr>
<td>4/M/49</td>
<td>8</td>
<td>C, M Pred, 20 mg QOD (4 wk) MMF, 1500 mg/d (8 mo)</td>
<td>Etan</td>
<td>12/12</td>
<td>6/1</td>
</tr>
<tr>
<td>5/M/48</td>
<td>1</td>
<td>M Pred, 20 mg/d (4 wk) AZA, 100 mg twice daily (4 wk)</td>
<td>Etan</td>
<td>6/5</td>
<td>11/6</td>
</tr>
<tr>
<td>6/M/59</td>
<td>9</td>
<td>C Pred, 20 mg/d (7 y)</td>
<td>Etan</td>
<td>30/9</td>
<td>3/1</td>
</tr>
<tr>
<td>7/F/50</td>
<td>4</td>
<td>C, M Clopetasol, 0.05%, cream (4 y)</td>
<td>Etan</td>
<td>21/20a</td>
<td>23/13a</td>
</tr>
<tr>
<td>8/M/46</td>
<td>1.5</td>
<td>C, M Pred, 20 mg QOD (18 mo) Nystatin suspension (10 mo) Clobetasol, 0.05%, solution (10 mo)</td>
<td>Etan</td>
<td>8/6</td>
<td>12/4</td>
</tr>
</tbody>
</table>

Abbreviations: AZA, azathioprine; C, cutaneous; Dexa, dexamethasone solution; Etan, etanercept; DLQI, dermatology life quality index; ISR, injection site reaction; M, mucosal; MMF, mycophenolate mofetil; PGA, physician global assessment; Plac, placebo; Pred, prednisone; PV, pemphigus vulgaris; QOD, every other day.

a In the PGA scale, 0 indicates clear; 1, near clear; 2, mild disease; 3, moderate disease; and 4, severe disease.
b Week 8; patient withdrew at week 10 owing to hip fracture.
c Week 8.
d Patient began treatment with topical clobetasol ointment at week 13; lesion count at week 8 was 58.
e Week 2; patient withdrew at week 4 owing to PV flare.
his prednisone dose. There were no serious adverse events or laboratory abnormalities.

**Comment.** Previous case reports (6 total patients in 3 reports1-3) describe uniformly effective results for the use of etanercept in PV. Our randomized, controlled study suggests that the response to etanercept is heterogeneous, although the small sample size precludes definitive conclusions. We observed 2 meaningful responses in the 4 patients who received etanercept and completed the study, although the use of azathioprine 1 month before etanercept initiation confounds the results for 1 of these 2 patients. It is possible that a higher dose of etanercept (eg, 50 mg twice weekly) might have conferred additional efficacy. The apparent placebo response is complicated by concurrent initiation of topical therapy in one patient and a questionably meaningful improvement in the other.

One weakness of our study is the lack of a well-validated end point—we noted cases of discordance between changes in lesion number and physician global assessment. Since this study was designed, an international consensus statement has emerged regarding definitions of disease end points and response,4 and, in addition, 2 novel outcome instruments for PV have been partially validated.5

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**Author Contributions:** All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kimball. Acquisition of data: Fiorentino, Rehmus, and Kimball. Analysis and interpretation of data: Fiorentino, Garcia, Rehmus, and Kimball. Drafting of the manuscript: Fiorentino and Garcia. Critical revision of the manuscript for important intellectual content: Rehmus and Kimball. Statistical analysis: Rehmus. Administrative, technical, and material support: Garcia. Study supervision: Fiorentino, Rehmus, and Kimball.

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**Skin Conditions That Bring Patients to Emergency Departments**

Skin diseases are common in the general population. The prevalence of dermatologic conditions that require medical treatment is estimated to range from 19% to 27%, with acne and eczema being the most common skin diseases.1,2 Yet, skin complaints account for only about 7% of all outpatient clinic visits,3 possibly because of the benign nature (both the true and the perceived) of most skin conditions. Perhaps this, as well as the low acute mortality of common dermatologic conditions, could also explain the lack of studies on emergency department (ED) visits that are attributable to skin diseases. Our study aimed to fill this gap and looked at the epidemiology of ED visits due to skin conditions.

**Methods.** The database used for this study was the National Ambulatory Care Records System, which is managed by the Canadian Institute for Health Information. The National Ambulatory Care Records System is a clinical administrative database with information on patient visits to EDs and day surgery units. It includes basic demographic, clinical, and administrative data.

For the study, we selected the records of patients who visited Ontario EDs between April 1, 2002, and March 31, 2007, and had a principal diagnosis of “diseases of the skin and subcutaneous tissue” (International Statistical Classification of Diseases, 10th Revision, codes L00-L99). Note that diagnoses recorded in this database are predominantly made by ED physicians, and it is impossible to discern whether the patient was seen by dermatology consulting services during the visit.

Statistical analysis of the data was performed using SAS software (Version 9.1; SAS Institute Inc, Cary, North Caro-