Treatment of Hidradenitis Suppurativa With Etanercept Injection

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**Objectives:** To observe the effects of etanercept treatment on the cutaneous manifestations of hidradenitis suppurativa (HS) and to evaluate physician and patient global assessment scores of cutaneous manifestations.

**Design:** Single-center, randomized, prospective, double-blind, placebo-controlled study.

**Setting:** Academic dermatology practice.

**Patients:** Twenty patients with active moderate to severe HS who fulfilled all inclusion criteria.

**Intervention:** Etanercept, 50 mg, or placebo was administered subcutaneously (SC) twice weekly for 12 weeks. After 12 weeks, all patients received open-label etanercept, 50 mg, SC twice weekly for 12 more weeks.

**Main Outcome Measures:** Primary end point: physician global assessment of HS as clear or mild at week 12. Secondary end points: patient global assessment and Dermatology Life Quality Index (DLQI).

**Results:** There was no statistically significant difference among physician global assessment, patient global assessment, and DLQI at 12 or 24 weeks between treatment and placebo groups \((P > .05\) for all comparisons).

**Conclusions:** Etanercept, 50 mg, SC administered twice weekly did not have significant efficacy in the improvement of HS. In light of our negative results, as well as those of previous studies, we suggest that future studies focus on other agents for the treatment of HS.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00949546

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HIDRADENITIS SUPPURATIVA (HS), a debilitating disease, is characterized by follicular occlusion resulting in recurrent painful abscesses, nodules, fistulas, and scarring.\(^1\) With numerous aspects of disease pathogenesis still poorly understood, it is not surprising that HS currently lacks a consistently effective treatment. Antibiotics (ie, clindamycin and tetracycline), antiandrogens, retinoids, immunosuppressive agents, zinc, irradiation, and surgical interventions have been used for HS therapy; however, none of these therapies consistently cause disease improvement, and none result in resolution.\(^2\) Recent studies have shown promising results with the use of anti–tumor necrosis factor (TNF) biologic agents. By suppressing TNF, a key inflammatory mediator, anti-TNF agents may prevent uncontrolled and/or chronic inflammation, thereby decreasing subsequent scarring and fistula formation.\(^3\) Three anti-TNF agents, etanercept, infliximab, and adalimumab, are currently being evaluated for use in HS therapy.

Etanercept, a dimeric human TNF receptor with greater affinity than natural monomeric receptors for TNF, is currently approved by the US Food and Drug Administration for treatment in the United States of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis. Studies have also documented improvement in HS disease activity score and Dermatology Life Quality Index\(^4\) (DLQI) with etanercept therapy.\(^5,6\) However, a recent study\(^7\) failed to find clinically significant efficacy of 50-mg/wk subcutaneous (SC) administration of etanercept for 12 weeks. Infliximab, a chimeric (murine-human) anti-TNF IgG1 monoclonal antibody, and adalimumab, a fully human monoclonal IgG1 antibody, have also been shown to improve HS.\(^8-11\) Adalimumab and infliximab have been associated with a higher dropout rate during rheumatoid arthritis studies owing to adverse effects.\(^12\) Also, infliximab has been linked with severe al-
higher dose of etanercept for a longer period of time.

cept, 50 mg, twice weekly for an additional 3 months.

weekly for 3 months, followed by open-label SC etaner-
cept's role in HS therapy and to determine if efficacy and
safety of treatment is dose or time dependent, we chose
to conduct a double-blind, placebo-controlled study in

inclusion or exclusion of patients. Patients were seen
to the clinic for a screening visit, baseline visit, and visits at 2,

enrolled over a 6-month enrollment period. Patients were seen
at a university department of dermatology. Twenty patients were
enrolled over to open-label SC etanercept, 50 mg, administered twice
weekly to all patients for 12 more weeks. The study took place
over to open-label SC etanercept, 50 mg, administered twice
weekly or SC placebo administered twice weekly for 12 weeks and then a cross-

This was a randomized, double-blind, placebo-controlled trial of SC etanercept, 50 mg, administered twice weekly or SC placebo administered twice weekly for 12 weeks and then a cross-

had a higher rate of granulomatous infections and Listeria monocytogenes infection compared with etanercept. In an effort to further elucidate etanercept's role in HS therapy and to determine if efficacy and safety of treatment is dose or time dependent, we chose to conduct a double-blind, placebo-controlled study in which SC etanercept, 50 mg, was administered twice weekly for 3 months, followed by open-label SC etanercept, 50 mg, twice weekly for an additional 3 months. In contrast to previous studies, this was a standardized higher dose of etanercept for a longer period of time.

STUDY PARTICIPANTS AND DESIGN

Institutional review board approval was obtained, and all patients gave informed consent before participation. Patients were eligible if they met the criteria specified in Table 1.

METHODS

END POINTS

The primary end point was the physician global assessment of HS as clear or mild at week 12 (Table 2). A single dermatologist (D.R.A.), who was blinded to the patient's group status, evaluated all patients. The secondary end points were patient global assessment of HS lesions on a scale from 0 (good) to 5 (severe). Patients also evaluated HS pain on a scale from 0 (none) to 5 (severe). Patients also completed the DLQI questionnaire.

STATISTICAL ANALYSIS

The primary end point was a determination of clear or mild on the physician global assessment of HS at week 12, which was compared between the treatment and placebo groups using the Fisher exact \( \chi^2 \) test. The secondary ordinal outcomes were compared between the 2 groups using the Mantel-Haenszel exact \( \chi^2 \) test. The number of affected locations was also summarized using means and standard deviations. Comparisons were reported at 12 and 24 weeks. All testing was 2 sided with a .05 significance level.
A total of 20 patients were enrolled, 10 receiving placebo and 10 receiving etanercept during the initial 12 weeks (Figure and Table 3). The only adverse drug reactions reported were mild injection site reactions. No severe adverse drug reactions were reported in any of the patients throughout the study.

At 12 and 24 weeks, there was no statistically significant difference in physician global assessment between treatment and placebo groups ($P > .99$ for all comparisons). There was also no statistically significant difference between treatment and placebo groups in physician-assessed pain ($P = .78$, 12 weeks; $P = .53$, 24 weeks), erythema ($P > .99$, 12 weeks; $P = .33$, 24 weeks), or discharge ($P = .45$, 12 weeks; $P > .99$, 24 weeks).

There was no statistically significant difference in disease activity score in 6 of 10 patients. Both of these studies had an open-label design without a control group and therefore may have been subject to evaluator and/or patient bias or placebo effect.

Both patients and dermatologists describe HS as a “heart-sink disease”1,17 because of its significant morbidity18 and lack of effective treatment. Affecting 1% to 4% of the population,19,20 HS can cause considerable physical pain from abscesses and fistulas as well as psychosocial trauma from disfiguring lesions, malodorous discharge, and false associations with lack of hygiene or socially unacceptable behavior.17 Our study demonstrates that twice-weekly SC administration of 50 mg of etanercept, a soluble dimeric human TNF receptor, is well tolerated in patients with HS but does not cause significant improvement in HS.

In support of our findings, Lee et al7 showed minimal evidence of clinically significant efficacy of open-label SC administration of etanercept, 50 mg/wk, for 12 weeks in the treatment of HS. Only 3 of 15 patients demonstrated a 50% reduction in the physician global assessment score. Patient-reported outcomes measured by DLQI showed a statistically significant improvement with etanercept therapy, but this finding was determined to have minimal clinical significance.

In contrast to our results, 2 uncontrolled prospective studies demonstrated a clinically significant benefit of etanercept for HS therapy.5,6 Cusack and Buckley6 administered SC etanercept, 50 mg/wk, to 6 women and then increased the SC dose to 100 mg/wk in 2 of the patients. Treatment duration varied with each subject. Response rates were determined by a disease activity score with 4 of 5 evaluable patients demonstrating over 50% improvement. One of the patients reported a greater than 50% improvement only after her dose was increased to 100 mg/wk. Giamarellos-Bourboulis et al5 administered SC etanercept, 50 mg/wk, for 12 wks and reported a 50% improvement only after her dose was increased to 100 mg/wk.

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**Table 3. Demographic Characteristics of Subject Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=10)</th>
<th>Etanercept (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mean</td>
<td>36.7</td>
<td>40.0</td>
</tr>
<tr>
<td>BMI, mean</td>
<td>32.1</td>
<td>33.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Corticosteroids only (pred or dexa)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Isotretinoin only</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroids and isotretinoin</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); dexa, dexamethasone; pred, prednisone.

*Unless otherwise indicated, data are reported as number of patients.

*One patient’s age in the etanercept treatment group was unknown.

*Each patient’s medication history was assessed for the following: pred, dexamethasone, mycophenolate, cyclophosphamide, methotrexate, acitretin, isotretinoin, etanercept, infliximab, and adalimumab. All previous medication regimens were terminated at least 30 days prior to the start of the study.
sample sizes and a predominance of female subjects compared with our study.

No data exist regarding a possible sex difference in HS response to etanercept therapy. In a study investigating etanercept treatment of psoriasis,23 etanercept was suggested to be more effective in patients with a lower body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). The mean BMI in our study was 32.8, which falls in the obesity range (BMI >30). Elevated BMIs may have decreased the effectiveness of etanercept in our study. Nevertheless, some studies have reported that more than 75% of their patients with HS were obese, and so an effective treatment for HS should result in disease improvement regardless of patient weight.

Current research is under way examining 2 other anti-TNF agents, infliximab and adalimumab. Unlike etanercept, infliximab and adalimumab are commonly used to treat granulomatous chronic inflammatory disease such as Crohn disease, a condition often coexistent with HS. These biologic agents are potentially more efficacious in HS treatment than etanercept: recent data have shown encouraging results. Improvement in HS after infliximab therapy has been reported in several trials and case studies, but some studies have questioned infliximab’s long-term efficacy. Recently, a prospective, double-blind, placebo-controlled, phase II study of infliximab demonstrated drug safety and significant improvement in Hidradenitis Suppurativa Severity Index and DLQI. Recent studies have also shown promising improvement of HS with adalimumab treatment. Further research examining adalimumab efficacy in a larger sample for optimal dose and long-term efficacy and safety is needed.

In conclusion, to our knowledge, this is the first double-blind, placebo-controlled study examining SC administration of etanercept, 50 mg twice weekly, in the treatment of HS. Although we found etanercept to be well-tolerated among all patients, it did not have significant efficacy in the improvement of HS. In light of our negative results, as well as those of previous studies, we suggest that future studies focus on other agents for the treatment of HS.

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Author Contributions: Dr Adams had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Adams and Anderson. Acquisition of data: Adams and Anderson. Analysis and interpretation of data: Adams, Yankura, Fogelberg, and Anderson. Drafting of the manuscript: Adams, Yankura, Fogelberg, and Anderson. Critical revision of the manuscript for important intellectual content: Adams, Yankura, Fogelberg, and Anderson. Obtained funding: Adams. Administrative, technical, and material support: Adams, Fogelberg, and Anderson. Study supervision: Adams and Anderson.

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REFERENCES