Treatment of Hidradenitis Suppurativa With Etanercept Injection

David R. Adams, MD, PharmD; Jessica A. Yankura, BS; Anneli C. Fogelberg, MD; Bryan E. Anderson, MD

Objectives: To observe the effects of etanercept treatment on the cutaneous manifestations of hidradenitis suppurative (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.\(^8,9,10,11\) 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. In contrast to previous studies, this was a standardized trial of SC etanercept, 50 mg, administered twice weekly for 12 weeks and then a crossover to open-label SC etanercept, 50 mg, twice weekly for an additional 3 months. The study took place over to open-label SC etanercept, 50 mg, administered twice weekly for 12 more weeks. The study took place at a university department of dermatology. Twenty patients were enrolled over a 6-month enrollment period. Patients were seen at the clinic for a screening visit, baseline visit, and visits at 2, 6, 12, 18, and 24 weeks for evaluation of vital signs, weight, height, disease improvement or progression, adverse effects, drug

METHODS

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.

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 crossover to open-label SC etanercept, 50 mg, administered twice weekly to all patients for 12 more weeks. The study took place at a university department of dermatology. Twenty patients were enrolled over a 6-month enrollment period. Patients were seen at the clinic for a screening visit, baseline visit, and visits at 2, 6, 12, 18, and 24 weeks for evaluation of vital signs, weight, height, disease improvement or progression, adverse effects, drug

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.4 Patients were carefully assessed for all adverse events related or unrelated to etanercept at each visit.

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-squared test. The secondary ordinal outcomes were compared between the 2 groups using the Mantel-Haenszel exact chi-squared 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.

Table 1. Inclusion and Exclusion Criteria for Participation

| Inclusion Criteria for All Participants |
| Age ≥18 y at time of screening |
| Chronic HS for > 6 mo defined as tender and/or painful red nodules and/or plaques (confluent nodules) with or without scarring, foul odor, or draining sinuses clinically consistent with HS |
| Active disease localized to skin folds, including any of the axillae, breasts, abdomen, and groin |
| Exclusion Criteria |
| Concurrent active infections including tuberculosis or presence of severe comorbidities including human immunodeficiency virus, diabetes mellitus requiring insulin, congestive heart failure, myocardial infarction, unstable angina pectoris, uncontrolled hypertension, oxygen-dependent severe pulmonary disease; history of TB or TB exposure, chronic hepatitis B or C, or systemic lupus erythematosus; history of multiple sclerosis, transverse myelitis, optic neuritis, or epilepsy; or history of cancer within 5 y except cutaneous basal cell, cutaneous squamous cell, or in situ cervical carcinoma |
| Known hypersensitivity to etanercept or any of its components |
| Currently enrolled or enrolled within 90 d prior to study entry in any trial of HS; undergoing any concurrent therapy or therapy 30 d prior to study entry with systemic corticosteroids, systemic immunosuppressants, systemic retinoids, or anti-TNF agents |
| Known hypersensitivity to etanercept or any of its components |
| Recent history of TB or TB exposure, chronic hepatitis B or C, or systemic lupus erythematosus; history of multiple sclerosis, transverse myelitis, optic neuritis, or epilepsy; or history of cancer within 5 y except cutaneous basal cell, cutaneous squamous cell, or in situ cervical carcinoma |

Table 2. Physician Global Assessment of Hidradenitis Suppurativa Lesions

<table>
<thead>
<tr>
<th>Score</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Complete clear except for residual scarring</td>
</tr>
<tr>
<td>1</td>
<td>Mild HS</td>
</tr>
<tr>
<td>2</td>
<td>Moderate HS</td>
</tr>
<tr>
<td>3</td>
<td>Severe HS</td>
</tr>
</tbody>
</table>

Abbreviations: HS, hidradenitis suppurativa; TB, tuberculosis; TNF, tumor necrosis factor.

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<td>1</td>
<td>Mean score 1, most lesions, for pain, erythema, and discharge</td>
</tr>
<tr>
<td>2</td>
<td>Mean score 2, most lesions, for pain, erythema, and discharge</td>
</tr>
<tr>
<td>3</td>
<td>Mean score 3, most lesions, for pain, erythema, and discharge</td>
</tr>
</tbody>
</table>

Abbreviations: HS, hidradenitis suppurativa; SGA, static global assessment (averaged over all lesions); TB, tuberculosis; TNF, tumor necrosis factor.

AGERIC REACTIONS and has a higher rate of granulomatous13,14 and has 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.

accountability, and concomitant medication treatment. Etanercept was also dispensed at these visits. No intranasal corticosteroids were administered throughout the study.

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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 patient global assessment (P = .41) or patient pain from HS at 12 (P = .77) or 24 weeks (P > .99). Finally, there was no statistically significant difference between groups in DLQI (P = .12, 12 weeks; P = .47, 24 weeks).

Both patients and dermatologists describe HS as a “heart-sink disease” because of its significant morbidity and lack of effective treatment. Affecting 1% to 4% of the population, 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. 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.

To our knowledge, our trial is the first double-blind, placebo-controlled study to examine etanercept treatment for HS. We believe it is also the first to examine a standardized higher dose of SC etanercept (50 mg twice weekly) for a longer period of time (24 weeks). An additional strength of our study is a more comprehensive evaluation of disease status, recommended by hidradenitis Suppurativa Foundation Inc and previous studies, including assessment of the anatomic regions involved, both patient and physician global assessment scores, and DLQI. The greatest limitations of our study are a small sample size (which might have limited statistical power to evaluate significance) and a homogeneous racial population.

In support of our findings, Lee et al 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. Cusack and Buckley 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 al administered SC etanercept, 50 mg/wk, for 12 wks and reported a 50% improvement 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. Furthermore, each of these studies had slightly smaller samples.
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). 7 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, 24, 25 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. 3, 8-11 Improvement in HS after infliximab therapy has been reported in several trials and case studies, 8-10 but some studies have questioned infliximab's long-term efficacy. 13, 14 Recently, a prospective, double-blind, placebo-controlled, phase 2 study of infliximab demonstrated drug safety and significant improvement in Hidradenitis Suppurativa Severity Index and DLQI. 19 Recent studies have also shown promising improvement of HS with adalimumab treatment. 3, 11 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, 7 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


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