Infliximab: A Treatment Option for Ulcerative Pyoderma Gangrenosum

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Abstract and Introduction

Abstract

As a tumor necrosis factor-alpha antagonist, infliximab is approved by the United States Food and Drug Administration for the treatment of rheumatoid arthritis and Crohn's disease. Infliximab has been used to treat a variety of dermatological diseases. Among these is pyoderma gangrenosum (PG), an uncommon inflammatory disorder characterized by painful skin ulcers. Often treated with corticosteroids, antibiotics with anti-inflammatory properties, and/or immunosuppressive medications, PG may be difficult to treat. The authors performed a retrospective analysis of patients with refractory PG treated with infliximab at a dose of 5mg/kg. Five patients were treated. Infliximab was efficacious in all, with healing of 12 of 13 ulcers in a mean time of 12.2 weeks. Patients received a range of one to three infusions (mean 1.8). In conclusion, infliximab is a treatment option for PG.

Introduction

Infliximab (Remicade®, Centocor Inc., Malvern, Pennsylvania) is a chimeric monoclonal antibody with high affinity for tumor necrosis factor-alpha (TNFa). The United States Food and Drug Administration (FDA) has approved infliximab for the treatment of rheumatoid arthritis and Crohn's disease. Infliximab appears to be efficacious in the treatment of a variety of inflammatory dermatological diseases, such as psoriasis, subcorneal pustular dermatosis, hidradenitis suppurativa, acute graft vs. host disease, Behçet's disease, refractory sarcoidosis and orofacial and perineal cutaneous Crohn's disease. Additionally, recent reports suggest its utility to treat pyoderma gangrenosum.

Pyoderma gangrenosum (PG) is a rare idiopathic inflammatory disease of undetermined cause. Most commonly affecting adults between 40 and 60 years of age, PG is characterized by erythematous, edematous, undermined, necrotic skin ulcers. The recurring and destructive ulcerations may begin as pustules, rapidly develop into necrotic ulcers with irregular borders, and may resolve with cribriform scars. PG is associated with certain systemic disorders in up to 75 percent of patients, most commonly inflammatory bowel disease. Other common associated conditions include rheumatoid or seronegative arthritis, monoclonal gammopathy, and hematologic malignancies.

PG is often found to localize at the site of trauma or an operative procedure, a response termed pathergy. Susceptible patients may mount an inappropriate cellular immune response to the tissue that has been antigenically modified as a result of trauma or operation. As PG is often mistaken for an infectious process, it may be mistreated with debridement and antibiotics.

Therapy includes corticosteroids, antibiotics with anti-inflammatory properties, and/or immunosuppressive medications. With mild disease, topical or intralesional steroids are useful but with more severe disease, systemic therapies are needed. PG is often refractory to treatment and a host of treatments, including cyclosporine, mycophenolate mofetil, methotrexate, and chlorambucil, has been reported. Infliximab may be a potentially useful treatment for PG. The authors report their experience with five patients with PG treated with infliximab.

Methods and Results

Methods

A retrospective chart review was performed for patients who received infliximab for PG at the University of Miami Department of Dermatology (Miami, Florida). Demographic and disease-specific data, including sex, age, previous treatments, adjunctive medications, and therapeutic response, were tabulated (Table 1). Ulcer size was recorded before and after treatment.

Results

A total of five patients with 13 ulcers were treated with infliximab. Their mean age was 60 (range 35 to 94 years of age). The mean initial size of the ulcers was 6.4cm². The mean disease duration was 6.6 months (range 1 to 17 months) (Table 1). Past therapies
included oral and intravenous antimicrobials; oral, intralesional, and intravenous steroids; and colchicine, pentoxifylline, cyclosporin A, stanozolol, clofazimine, mycophelate mofetil, and dapsone. At the time of initial administration, all patients were free of known acute or chronic infections and had negative chest X-rays and/or purified protein derivative (PPD) tests for tuberculosis. Associated conditions included ulcerative colitis, hidradenitis suppurativa, and seronegative arthritis, among others (Table 1).

All patients received initial infusions of infliximab 5mg/kg. The infusions were given over a several hour time period. Of the five patients, the number of infusions ranged from one to three (Figure 1). Two patients (Patients 1 and 2) received three treatments, two patients (Patients 3 and 5) were administered a single infusion, and the final patient (Patient 4) received two treatments, the second of which was discontinued after the patient experienced flushing and pruritus. These symptoms subsided after the infliximab infusion was stopped. Adjunctive medications included cyclosporine A, systemic steroids, and topical tacrolimus.

Figure 1. This figure illustrates the patients’ response times (in weeks) to resolution of PG ulcer post-infliximab infusion therapy.

All patients and 12 of 13 ulcers healed (Table 1). The mean time to heal was 12.2 weeks. Marked improvement occurred within one month. One patient indicated that the pain associated with the lesion had decreased by 50 percent within 24 hours of treatment, and the ulcer reduced in size by 50 percent 72 hours postinfusion. Interestingly, in that patient, repeated infusions were required for complete resolution. Although the PG ulcer of Patient 4 resolved with the first infusion of infliximab, treatment for a subsequent ulcer was discontinued after the patient experienced flushing and pruritus. These symptoms subsided after the infliximab infusion was stopped, and the ulcer eventually healed with systemic steroids. No other adverse effects occurred.

Table 1 and Figure 1 summarize the outcome of the five patients. Figures 2A and B are of Patient 4 before and after treatment with infliximab.
Figure 2. These photographs show an 81-year-old man who developed pathergy and ulcer formation after an abdominal lipectomy. A) This is the patient after a course of oral steroids, which he did not tolerate, and prior to infliximab. B) This is the patient nine weeks after a single infusion of infliximab with complete healing.

Discussion

Five patients with 13 ulcers diagnosed with PG were treated with infliximab. All patients were unresponsive to or did not tolerate previous treatment, and the mean duration of disease was 6.6 months (range 1-17 months). Patients received a range of 1 to 3 infusions (mean 1.8). All patients and 12 of 13 ulcers healed with the infliximab monotherapy (2 patients) or as an adjuvant therapy (3 patients), with a mean time to heal of 12.2 weeks.

Infliximab is a chimeric monoclonal antibody that irreversibly binds to TNFα with a high affinity, thereby preventing TNFα from binding to its receptors. Infliximab is composed of the human immunoglobulin IgG constant region combined with the variable region of the mouse TNF monoclonal antibody. Produced by macrophages, neutrophils, eosinophils, and lymphocytes, TNFα acts as an inflammatory cytokine eliciting a variety of responses, including activation of other proinflammatory cytokines, which include interleukin-1 (IL-1), IL-6, and IL-8. This results in recruitment, migration, adhesion, and activation of other neutrophils, lymphocytes, and eosinophils and also induction of CD4 T-cell and macrophage cytotoxicity,[19-21] which, in turn, results in inflammation and tissue destruction.

Infliximab is usually tolerated well. Several adverse reactions have been reported, including headache, nausea, upper respiratory infections, abdominal pain, fatigue, and fever, which are some of the more commonly experienced reactions. In this series, one patient (Patient 4) developed flushing and pruritus, requiring discontinuation of therapy, whereby the symptoms subsided.

The long-term risks associated with infliximab are still largely undetermined. Although increases in tuberculosis, upper respiratory tract infections, and urinary tract infections have been reported, differences in mortality rates or severe infections following infliximab therapy have not.[22] It is critical to obtain a chest radiograph and PPD prior to treatment, as the authors had in their patients. Infliximab may stimulate the production of antinuclear antibodies and antibodies to double-stranded DNA, but even in those cases development of clinical lupus syndrome is rare.[23]

In conclusion, the authors report the clinical success of infliximab as both monotherapy and as adjuvant therapy for patients with PG. The TNFα antagonist provided rapid improvement and eventual resolution of the lesions associated with PG. However, larger, controlled studies are required to further examine the optimal dosing schedule, duration of improvement, and long-term effects of infliximab therapy.

Tables

Table 1. Patient demographics, prior and current therapies, and response to infliximab 5mg/kg

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Disease Duration (months)</th>
<th>Affected Areas</th>
<th>Previous Treatment</th>
<th>Adjunctive Treatment</th>
<th>Initial Ulcer Size (cm x cm)</th>
<th>No. of Infusions</th>
<th>Resolution of Ulcer (weeks after first infusion)</th>
<th>Associated Conditions</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>94/Female</td>
<td>9</td>
<td>Left lower extremity</td>
<td>Colchicine, IV steroids, Stanozolol</td>
<td></td>
<td>1.5 x 1.5</td>
<td>3</td>
<td>24</td>
<td>Hypertension, Hypothyroid</td>
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<tr>
<td>2</td>
<td>35/Male</td>
<td>1</td>
<td>Right posterior lower extremity</td>
<td>Pentoxifylline</td>
<td>Oral steroids</td>
<td>Oral steroids</td>
<td>1.5 x 2.5</td>
<td>0.5 x 0.05</td>
<td>1.0 x 1.0</td>
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<td>3</td>
<td>50/Female</td>
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<td>Right medial thigh</td>
<td>Pentoxifylline</td>
<td>Dapsone</td>
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<td>4</td>
<td>81/Male</td>
<td>4</td>
<td>Abdomen post lipectomy</td>
<td>Pentoxifylline</td>
<td>Oral steroids</td>
<td>IV steroids</td>
<td>4.0 x 2.0</td>
<td>3.0 x 1.5</td>
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<tr>
<td>4a</td>
<td></td>
<td></td>
<td></td>
<td>Pentoxifylline</td>
<td>Oral steroids</td>
<td>Oral steroids</td>
<td>2.1 x 1.8</td>
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<td>5</td>
<td>40/Female</td>
<td>17</td>
<td>Left lateral leg</td>
<td>Pentoxifylline</td>
<td>Cyclosporine</td>
<td>Oral steroids</td>
<td>Oral steroids</td>
<td>11.5 x 8.6</td>
<td>3.5 x 3.5</td>
</tr>
</tbody>
</table>

* 4a represents Patient 4 who underwent treatment for a subsequent ulcer. This infusion was stopped due to side effects, and the ulcer eventually healed with systemic steroids.

References

Reprint Address

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