Mycophenolate Mofetil as Therapy for Pyoderma Gangrenosum

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Background: Pyoderma gangrenosum is an ulcerative condition that may be associated with inflammatory bowel disease or inflammatory arthritis. In addition to local wound care, management often includes the use of systemic corticosteroids or systemically administered immunomodulatory agents.

Observations: We retrospectively analyzed 7 patients with pyoderma gangrenosum who were treated with mycophenolate mofetil. Patients were included if they had a diagnosis of pyoderma gangrenosum and were treated with mycophenolate mofetil for at least 2 uninterrupted months. Improvement was based on reduction in lesion size or decrease in concomitant therapy. Overall, 6 of 7 patients had some reduction in ulcer size while receiving mycophenolate mofetil therapy, and 4 of 7 completely healed. However, responsiveness was inadequate in 3 patients. Two discontinued mycophenolate mofetil for alternate therapy, and the third required the addition of dapsone and infliximab for complete healing. The only adverse event observed in our analysis attributed to mycophenolate mofetil therapy was transient anemia.

Conclusions: Mycophenolate mofetil may be beneficial as an immunomodulatory agent in selected patients with pyoderma gangrenosum. Further controlled trials are warranted to define its place among the therapeutic options for this rare disease.

Arch Dermatol. 2009;145(7):781-785

PYODERMA GANGRENOSUM (PG) is a rare disease of the skin manifesting as painful ulcers. Most commonly found on the lower extremities, PG is also seen peristomally in approximately 13% to 15% of patients. Systemic manifestations are possible and can include fever, malaise, arthralgia, and myalgia.1-3 In approximately 50% of patients with PG, an associated condition is found. The most frequent associations are inflammatory bowel disease or arthritis (most commonly rheumatoid arthritis–like polyarthritis) myeloproliferative disease or monoclonal IgA gammopathy. The activity of the associated systemic disease may or may not reflect the clinical activity of PG.1,4

There are no laboratory findings or imaging studies that are diagnostic of PG. Testing to exclude infection, neoplasm, panniculitis, prothrombotic state, inflammatory vasculitis, or arterial or venous insufficiency is typically performed before a diagnosis of PG is made.5,6

Therapy is centered on wound care, treatment of secondary infection, and the addition of local or systemic immunosuppressive therapy. In mild cases, local topical therapy may prove effective, including cromolyn sodium, calcineurin inhibitors, or superpotent corticosteroids or intraleisional corticosteroids. However, most patients will require systemic treatment, and medium- to high-dose corticosteroids are traditionally used as initial therapy. Frequently, a corticosteroid-sparing agent is used to ameliorate the adverse effects associated with systemic corticosteroid use. To our knowledge, only one placebo-controlled blinded study has been performed in patients with PG. Brooklyn et al7 evaluated the use of infliximab vs placebo in patients with PG and found that 46% of patients in the infliximab arm had improved at 2 weeks compared with 6% who received placebo. Otherwise, case series and individual case reports dominate the literature and have detailed the usefulness of cyclosporine, azathioprine, methotrexate, etanercept, adalimumab, tacrolimus, plasmapheresis, intravenous immunoglobulin, cyclophosphamide, chlorambucil, dapsone, interferon alfa, clofazimine, and mycophenolate mofetil.3-10

Herein, we discuss our experience in a series of 7 patients with PG who were treated with mycophenolate mofetil.

Methods

We reviewed all medical records of patients with PG in a university-affiliated private practice. All patients had clinically typical ulcerations, histopathologic findings consistent with a diagnosis of PG, and laboratory test results...
that did not reveal an alternative explanation for ulceration. The study design was approved by the Institutional Review Board at the University of Louisville.

Patients were included in the study if they met criteria for the diagnosis of PG, received mycophenolate mofetil specifically for the diagnosis of PG, and underwent therapy with mycophenolate mofetil for a minimum of 2 uninterrupted months. We excluded any patients with equivocal diagnoses or those who were lost to follow-up.

Data were obtained regarding age, sex, medical history, medication use, laboratory tests and imaging, microbiologic cultures, and biopsy results. We evaluated the time of initial PG, all therapies associated with PG, and the response to any therapy before the initiation of treatment with mycophenolate mofetil. We calculated the size of each ulceration in square centimeters, and when multiple ulcerations were present, we summed the areas of all ulcers to achieve a total area. Among patients receiving mycophenolate mofetil, we evaluated the change in size of ulcerations in terms of total change in square centimeters and percentage change since the initiation of mycophenolate mofetil therapy. We noted all instances when concomitant therapy other than mycophenolate mofetil was administered. Dosages of mycophenolate mofetil were noted, as well as time to response and any toxic effects of the use of the medication. Improvement was based on a decrease in ulcer size or reduction in concomitant immunosuppression level.

### RESULTS

Table 1 summarizes the characteristics of patients included in our analysis. Patient 5 has been previously described by Daniels and Callen.11 The 7 patients (4 women and 3 men) ranged in age from 18 to 75 years. Three patients had Crohn disease, and 1 patient had a history of sarcoidosis. Four patients were initially seen with lower extremity ulcerations, while 3 patients had lesions affecting the peristomal area or a midline laparotomy scar. Only 1 patient was naive to systemic therapy of any kind, and 2 patients had received only culture-directed antibiotics or vitamin and mineral dietary supplements. All other patients had received systemic treatment, including varying dosages and combinations of dapsone, minocycline hydrochloride, cyclosporine, azathioprine, and prednisone. Three of 4 patients treated with systemic immunosuppression had adverse effects related to the immunosuppressive agents before beginning mycophenolate mofetil therapy. Time from diagnosis of PG to treatment with mycophenolate mofetil ranged from 1 to 71 months.

Mycophenolate mofetil was started at a dosage of 0.5 g/d in 1 patient, and all other patients began therapy at a dosage of 1 g twice daily (Table 2). Maximum dosages of mycophenolate mofetil ranged from 0.5 g 4 times daily to 2 g twice daily (mode, 1.5 g twice daily). In addition, all patients used concomitant topical or systemic medications, which are listed in Table 2. Six of 7 patients showed reduction in ulcer size while receiving mycophenolate mofetil, and 4 of those patients completely healed. The Figure shows the response observed in patient 4 from the initiation of mycophenolate mofetil treatment through 23 weeks of therapy. The onset of response began at 4 to 12 weeks among those patients who responded to mycophenolate mofetil therapy. For 2 patients, mycophenolate

### Table 1. Patient Characteristics Before Treatment With Mycophenolate Mofetil

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age at Diagnosis, y</th>
<th>Associated Medical Condition</th>
<th>Location of PG</th>
<th>Previous Systemic Therapy [Related Toxic Effects if Present]</th>
<th>Duration of PG Before Treatment With Mycophenolate Mofetil, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/67</td>
<td>None</td>
<td>Right calf</td>
<td>Cyclosporine (100-200 mg once daily) [hypertension, decreased kidney function], prednisone (2.5 mg every other day to 100 mg once daily) [gastric ulcers, osteoporosis], dapsone (100 mg once daily), minocycline (100 mg once daily)</td>
<td>71</td>
</tr>
<tr>
<td>2/M/51</td>
<td>Crohn disease</td>
<td>Midline laparotomy scar, peristomal</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>3/M/30</td>
<td>Crohn disease</td>
<td>Peristomal</td>
<td>Culture-directed antibiotics</td>
<td>1</td>
</tr>
<tr>
<td>4/F/75</td>
<td>None</td>
<td>Right pretilbum</td>
<td>Ascorbic acid, zinc, culture-directed antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>5/F/18*</td>
<td>Crohn disease</td>
<td>Peristomal</td>
<td>Dapsone (50 mg once daily) [elevated LFTs], azathioprine (100 mg once daily) [leg cramps, elevated LFTs], prednisone (10-40 mg once daily), culture-directed antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>6/M/24</td>
<td>None</td>
<td>Left pretilbum, left calf</td>
<td>Cyclosporine (800 mg once daily), minocycline (100 mg twice daily), prednisone (10-40 mg once daily), culture-directed antibiotics</td>
<td>40</td>
</tr>
<tr>
<td>7/F/64</td>
<td>Sarcoidosis</td>
<td>Left leg</td>
<td>Cyclosporine (400 mg once daily) [elevated creatine kinase level], culture-directed antibiotics</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: LFTs, liver function test results; PG, pyoderma gangrenosum.

*Patient previously described by Daniels and Callen.11
mofetil was their only systemic therapy for PG. Patient 1 continued a regimen of prednisone while receiving mycophenolate mofetil treatment and was able to taper the prednisone dosage from 10 mg to 2.5 mg every other day.

Three patients had inadequate responses, defined as non-healing or worsening of PG while receiving mycophenolate mofetil therapy. Patient 2 initially had minimal response to mycophenolate mofetil as monotherapy and healed in approximately 16 months after the addition of dapsone and infliximab to his regimen. Patients 3 and 6 responded to adalimumab therapy. Patient 6 had minimal response with mycophenolate mofetil; maximal healing occurred after the addition of infliximab and dapsone.

Mycophenolate mofetil therapy was generally well tolerated, with 6 of 7 patients experiencing no attributable adverse effects. One patient experienced transient anemia, which reversed with a lower dosage of mycophenolate mofetil.

**COMMENT**

In 1997, mycophenolate mofetil was approved by the Food and Drug Administration as an immunosuppressant to prevent renal transplant rejection. Soon thereafter, its use was adapted to treat various autoimmune conditions, including rheumatoid arthritis and lupus nephritis. During the past decade, its use in dermatology has increased, and off-label applications have been reported in treating bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, psoriasis, atopic dermatitis, subacute cutaneous lupus, lichen planus, cutaneous Crohn disease, dermatomyositis, vasculitis, graft-versus-host disease, and sarcoidosis. Mycophenolate mofetil is a prodrug of mycophenolic acid and was created to increase the oral bioavailability of mycophenolic acid. After mycophenolate mofetil is absorbed, esterases in the blood, liver, and kidney convert mycophenolate mofetil to the active compound mycophenolic acid. Mycophenolic acid then undergoes glucuronidation in the liver, creating a metabolite that cannot penetrate cellular membranes, rendering the drug ineffective. However, the skin and gastrointestinal tract possess beta-glucuronidase, an enzyme that converts the drug back into the active form. Mycophenolic acid noncompetitively inhibits inosine monophosphate dehydrogenase and prevents the synthesis of xanthine-5-phosphate and guanine-5-phosphate, inhibiting the production of DNA and RNA. T cells and B cells are particularly affected because they lack a salvage pathway for purine synthesis and use a form of inosine monophosphate dehydrogenase that has a particular affinity for mycophenolic acid.
Although the pathogenesis of PG is unknown, evidence suggests that it is an abnormal response of the immune system to an unknown antigen, resulting in cutaneous ulceration. It is likely for this reason that immunosuppressant medications such as mycophenolate mofetil are effective in controlling PG.

To our knowledge, this is the largest published series of patients having PG treated with mycophenolate mofetil. Lee and Cooper described 4 patients having PG who were successfully treated with mycophenolate mofetil. In their series, dosages ranged from 0.5 g twice daily to 2.5 g/d. Three patients received prednisone concomitantly with mycophenolate mofetil therapy, and 1 patient received mycophenolate mofetil as monotherapy. Three patients completely healed, while 1 patient showed improvement in ulceration. Adverse events associated with therapy included headaches, palpitations, gastrointestinal upset, and staphylococcal and pseudomonal sepsis.

Multiple case reports have detailed success with the use of cyclosporine and mycophenolate mofetil for therapy-resistant PG. Nousari et al described a patient having PG that was refractory to treatment with azathioprine, dapsone, cyclophosphamide, and varying dosages of intralesional, oral, and intravenous corticosteroids. The patient began taking mycophenolate mofetil (0.5 g twice daily) in addition to her daily regimen of cyclosporine (5 mg/kg) and prednisone (1 mg/kg). The mycophenolate mofetil dosage was increased to 1 g twice daily, and healing began to occur within 5 weeks. The patient was almost completely healed by week 14. The therapy was well tolerated, without adverse effects.

Included in the present case series is a patient previously described by a colleague and one of us (J.P.C.) whose peristomal PG resolved in response to treatment with mycophenolate mofetil and topical tacrolimus ointment. Wollina and Karamfilov detailed their experience of therapy-resistant PG that improved after the use of mycophenolate mofetil, intravenous prednisolone, hyaluronic acid matrix, and subsequent autologous epithelial grafting. In 2007, Cummins et al published their findings with the use of intravenous immunoglobulin as adjuvant treatment with concomitant immunosuppressant therapy. Although they did not provide the exact therapeutic regimens of all patients, they described 2 patients in whom intravenous immunoglobulin and mycophenolate mofetil therapy resulted in healing.

High-dose corticosteroid therapy has been used to effectively control PG; however, adverse effects often become apparent when corticosteroids are used throughout the typically prolonged course of healing. In fact, a patient in our analysis experienced gastric ulcers and osteoporosis while receiving systemic prednisone therapy. In a series of 12 patients having PG treated with systemic corticosteroids, Holt et al found that 6 patients had corticosteroid-related complications and that 4 patients died as a result of therapy. Other systemic medications reported to be effective in PG have well-described toxic effects. In our series, we observed undesirable adverse effects associated with the use of cyclosporine, dapsone, and azathioprine before administration of mycophenolate mofetil. One patient in our series had a prior adverse reaction to infliximab therapy for Crohn disease, rendering it inappropriate treatment for subsequent development of PG. In a study by Brooklyn et al, 4 of 13 patients treated with infliximab had attributable adverse effects, resulting in the death of 1 patient.

Figure. Progression of mycophenolate mofetil therapy in patient 4 with pyoderma gangrenosum. A, Ulcer with violaceous border on the lower extremity before mycophenolate mofetil therapy. B, Ulcer on the lower extremity after 15 weeks of mycophenolate mofetil therapy. C, Healed ulcer on the lower extremity after 23 weeks of mycophenolate mofetil therapy.
Among our 7 patients treated with mycophenolate mofetil, the only adverse effect was transient anemia that stabilized after lowering the dosage. Commonly reported adverse effects include gastrointestinal tract abnormalities (nausea, vomiting, diarrhea, abdominal cramps, constipation, and bleeding) and genitourinary tract effects (urgency, frequency, dysuria, and sterile pyuria); less common are leukopenia, anemia, increased risk of infection, and induction of malignant neoplasm, which seem to be dose related.\textsuperscript{12,13} Periodic monitoring of complete blood cell count and clinical evaluation for signs of infection should be performed. In addition, the use of antacids, oral magnesium, and cholesteryamine resin decreases the bioavailability of mycophenolate mofetil.\textsuperscript{12} Increased risks of fetal loss and teratogenic effects have been noted in pregnant women receiving mycophenolate mofetil, and the Food and Drug Administration changed the pregnancy class of the drug from C to D in October 2007.

Our data suggest that mycophenolate mofetil may be a safe and effective immunosuppressant for PG and may be particularly beneficial in combination with other topical or systemic medications. We used it as first-line therapy in patients who were therapy resistant or who experienced adverse effects with prior therapies. All patients were also receiving some form of concomitant topical or systemic therapy; therefore, we cannot exclude the possibility that this treatment affected our results. Although not universally effective, the use of mycophenolate mofetil resulted in healing in most patients in this study. It is important to recognize publication bias regarding therapy for PG, because positive studies are frequently published and negative ones do not receive recognition. Our study is significant in that it details our experience with mycophenolate mofetil for treatment of PG regardless of success or failure. We acknowledge the inherent limitations of the retrospective nature of this review and would encourage a placebo-controlled double-blind study to further assess the efficacy of mycophenolate mofetil in treating PG.

Accepted for Publication: August 27, 2008.

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Author Contributions: Drs Eaton and Callen 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: Eaton and Callen. Acquisition of data: Eaton and Callen. Analysis and interpretation of data: Eaton and Callen. Drafting of the manuscript: Eaton and Callen. Critical revision of the manuscript for important intellectual content: Callen. Study supervision: Callen.

Financial Disclosure: Dr Callen receives honoraria from or serves as a consultant to Electrical Optical Sciences, Abbott Immunology, Amgen, Centocor, Steidel, and Medici; provides analysis of legal cases related to lupus erythematosus, dermatomyositis, and systemic therapies on occasion for the defense or plaintiff; and receives book royalties from Elsevier.

Disclaimer: Dr Callen is an associate editor of the Archives of Dermatology but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

REFERENCES