The Effectiveness of Mycophenolate Mofetil in Refractory Pyoderma Gangrenosum

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 32-year-old white woman with systemic lupus erythematosus presented with a 2-year history of refractory pyoderma gangrenosum on the left pretibial area. The lesion eroded to expose underlying tendons and muscles, and involvement of deep structures caused mononeuritis, with resultant unilateral foot drop and intractable pain. Therapeutic regimens that had been used during this 2-year period but had failed to arrest progression included the following: prednisone, 1 mg/kg per day; prednisone in combination with azathioprine, 2.5 mg/kg per day; dapsone, 100 mg/d; oral cyclophosphamide, 2 mg/kg per day; and intralesional triamcinolone acetonide injections. Three intravenous pulses of methylprednisolone, 1 g each, as well as 2 intravenous cyclophosphamide pulses, 500 mg per pulse, were given to the patient without additional improvement. Immediately prior to the initiation of the new therapeutic regimen, the patient had been treated with prednisone, 1 mg/kg per day, in conjunction with microemulsion cyclosporine, 5 mg/kg per day, for 4 months. All these therapeutic regimens had demonstrated an inability to induce healing of the lesion.

Results of a histological examination showed a neutrophil-rich dermal infiltrate and granulation tissue. Results of a direct microbiologic examination and cultures of multiple lesional skin biopsy specimens failed to demonstrate evidence of bacterial, viral, fungal, or mycobacterial infection. Findings from direct immunofluorescence studies of the skin were negative for vasculitis. Conventional radiographic, triphasic bone, and magnetic resonance imaging scans showed no evidence of osteomyelitis.

Antinuclear antibodies were detected at a titer of 1:80 with a fine speckled pattern. Evaluation for antiphospholipid antibodies, lupus anticoagulant Russell viper venom time, cryoglobulins, rheumatoid factor, complement, antineutrophil cytoplasmic antibodies, and serum protein immunoelectrophoresis levels were all within normal limits.

The results of the physical examination were remarkable for a 10-cm deeply ulcerated lesion on the patient's left pretibial area, with granulation tissue in the base and undermined violaceous borders (Figure 1). Small satellite cutaneous pustular lesions were intermittently observed during periods of active ulcer expansion. No regional lymphadenopathy was detected.

Corticosteroids and other immunomodulatory/immunosuppressive drugs are usually effective for the treatment of pyoderma gangrenosum. Intravenous methylprednisolone pulse therapy, oral cyclosporine, tacrolimus, and alkylating agents are usually effective therapeutic regimens for severe cases of pyoderma gangrenosum. The pa-
Pyoderma gangrenosum is a neutrophilic dermatosis characterized clinically by ulcerated plaques with erythematous and violaceous undermined borders. Although idiopathic cases are commonly found, this condition is frequently associated with inflammatory bowel disease, vasculitis, and autoimmune diseases. Numerous drugs have been reported as effective therapeutic agents for pyoderma gangrenosum. However, corticosteroids, cyclosporine, tacrolimus, alkylating agents, and antimetabolite agents are the only drugs that have been consistently demonstrated to be effective in the treatment of refractory pyoderma gangrenosum.1,2

Mycophenolate mofetil is an ethyl ester of mycophenolic acid with increased bioavailability. Mycophenolate mofetil is rapidly hydrolyzed and transformed in the liver into its active metabolite, mycophenolic acid. Mycophenolic acid is a product of numerous Penicillium species, although originally isolated as a fermentation product of Penicillium stoloniferum.

Mycophenolic acid has been used with good results and acceptable adverse effects for the treatment of moderate and severe psoriasis. These findings have been supported by several studies including open-label, long-term studies and a multicenter, double-blind, placebo-controlled trial.3-8 The questionable increased incidence of carcinogenicity and latent viral infections associated with the use of mycophenolic acid discouraged the continuation of studies of this drug for psoriasis. Careful review of these data demonstrated that all patients with psoriasis who developed herpes zoster infection and other viral and bacterial infections during therapy with mycophenolic acid had uncomplicated infectious disease and had been receiving dosages of mycophenolic acid higher than 3 g/d.4-8 Opportunistic infections have not been reported during therapy with mycophenolic acid.

Although a few patients with psoriasis treated with mycophenolic acid developed various cancers,5 this rate was no greater than that which would be expected in the general population.8 Topical mycophenolic acid has been demonstrated to be effective in the treatment of experimental allergic contact dermatitis.9 Clinical trials of topical mycophenolic acid or mycophenolate mofetil in patients with skin diseases have not been conducted yet.

Mycophenolate mofetil was synthesized to increase the bioavailability and to improve the immunosuppressive activity of mycophenolic acid. Mycophenolate mofetil is an immunomodulatory drug that is rapidly converted to mycophenolic acid after ingestion. In a noncompetitive fashion, mycophenolic acid selectively inhibits the type 2 isomerase of inosine monophosphate dehydrogenase in the de novo pathway of purine synthesis.10-12 This enzyme is primarily found in lymphocytes, and it is responsible for the conversion of inosine monophosphate into xanthine monophosphate, an intermediate metabolite in the synthesis of guanosine triphosphate. Lymphocytes minimally use the hypoxanthine/guanine phosphoribosyltransferase salvage pathway for purine synthesis, so that inhibition of the de novo pathway of purine synthesis would have a potent cytostatic effect in the nucleic acid synthesis of T and B lymphocytes. Thus, mycophenolic acid inhibits both lymphocyte proliferation and antibody formation. Mycophenolic acid also exerts its immunomodulatory effects through inhibiting the leukocyte recruitment and glycosylation of lymphocytic glycoproteins involved in their adhesion to endothelial cells.11

**Figure 2.** The patient after a 10-week trial of therapy with mycophenolate mofetil, 2 g/d for 5 weeks, reduced to 1 g/d after 5 weeks; cyclosporine, 5 mg/kg per day; and prednisone, 1 mg/kg per day.
Mycophenolate mofetil is rapidly absorbed and converted to mycophenolic acid after oral administration. Mycophenolic acid is nearly completely metabolized in the liver by glucuronosyltransferase, and its inactive glucuronide metabolite is primarily eliminated by renal excretion. β-D-Glucuronidase is an enzyme that exists in significant quantities in the skin in addition to other tissues, and it has the ability to convert the inactive mycophenolic acid glucuronide back into its active form, mycophenolic acid. This pharmacokinetic feature may be relevant in the therapy of dermatologic conditions. Mycophenolate mofetil’s pharmacokinetics appear not to be affected by the concomitant administration of cyclosporine. There is a decreased absorption of mycophenolate mofetil with the administration of cholestyramine, magnesium, and aluminum hydroxide antacids. Mycophenolic acid binds strongly to albumin. Studies in vitro have demonstrated that high concentrations of salicylate and furosemide can displace mycophenolic acid from albumin. The clinical implications of this finding are unknown.11

The usual dosage of mycophenolate mofetil is 1 g orally twice per day. The most common adverse effects are those related to the gastrointestinal tract, such as nausea, abdominal cramps, anorexia, vomiting, and diarrhea. These gastrointestinal adverse effects are usually mild and dose dependent, and may be observed in up to 20% of patients receiving mycophenolate mofetil at dosages of 2 g/d or lower. Mycophenolate mofetil therapy should be administered with caution in patients with active serious gastrointestinal system disease.

Mild to moderate leukopenia and anemia have been reported in less than 5% of patients treated with mycophenolate mofetil. An elevated incidence of opportunistic infections has also been reported. However, these hematologic and infectious complications have usually occurred only when mycophenolate mofetil dosages have exceeded 2 g/d. A slight elevation of the level of liver aminotransferases is expected, but this finding is usually not clinically significant and does not require dosage adjustment or discontinuation of mycophenolate mofetil therapy. There has been no increase in the incidence of clinically significant nephrotoxic, hepatotoxic, hypertensive, or neurotoxic effects when mycophenolate mofetil was used alone in patients with rheumatoid arthritis and when mycophenolate mofetil was used in combination with cyclosporine and corticosteroids in patients who have received transplants.

Formal monitoring guidelines for the use of mycophenolate mofetil have not been delineated, but periodic evaluation of complete blood cell count and liver enzyme, bilirubin, and creatinine levels should be done. The measurement of the inosine monophosphate dehydrogenase activity in whole blood may be useful for the evaluation of immunosuppression induced by mycophenolate mofetil. However, this test is not yet widely available in clinical laboratories.

A slightly increased incidence of lymphoproliferative disorders, such as lymphoma secondary to exposure to mycophenolate mofetil, has been suspected. However, the exact incidence of this complication is not yet established.

Mycophenolate mofetil was first approved by the Food and Drug Administration in 1995 for use in combination with cyclosporine and corticosteroids to prevent renal transplant rejection. Mycophenolate mofetil has also been used with good results in rheumatoid arthritis, bullous pemphigoid, systemic vasculitis and IgA nephropathy, pemphigus vulgaris, and liver and cardiac transplantation. The role of mycophenolate mofetil in immunologically mediated skin diseases seems to be promising, not only because of its efficacy but also owing to its relatively limited toxic effects. Mycophenolate mofetil should be considered an effective addition to the therapeutic armamentarium for recalcitrant pyoderma gangrenosum.

REFERENCES