OBSERVATION

Mycophenolate Mofetil as an Effective Corticosteroid-Sparing Therapy for Recalcitrant Dermatomyositis

Johnathon C. Edge, MD; J. David Outland, MD; Jennifer R. Dempsey, MD; Jeffrey P. Callen, MD

Background: Dermatomyositis (DM) is a multisystem idiopathic inflammatory disorder that most commonly affects the muscles and skin. Systemic corticosteroids are the mainstay of therapy but are limited by their long-term adverse effects.

Observations: We sought to evaluate the effectiveness of oral mycophenolate mofetil in patients with cutaneous lesions of DM recalcitrant to other therapies through an open-label retrospective medical chart review of patients in a university-affiliated private practice setting. Twelve patients with DM who had skin lesions recalcitrant to traditional therapies or who developed toxic effects from traditional therapies began mycophenolate mofetil treatment at doses ranging from 500 mg to 1 g twice a day. Response was based on improvement in skin disease as judged clinically, an increase in strength, and/or an ability to decrease or discontinue concomitant therapies. Improvement was seen in 10 of the 12 patients, most within 4 to 8 weeks. Most patients tolerated mycophenolate mofetil treatment without problem; however, 1 patient developed a B-cell lymphoma of the central nervous system, and another developed abnormal levels of hepatic enzymes along with urinary symptoms. Resolution of these toxic reactions occurred with cessation of mycophenolate mofetil treatment in each patient.

Conclusion: Mycophenolate mofetil may be an effective corticosteroid-sparing therapy for the treatment of some patients with DM.

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Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized clinically by proximal symmetric muscle weakness and 1 or more of the following cutaneous manifestations: heliotrope rash, Gottron papules, cuticular changes, a photodistributed erythema or poikiloderma, and a scaly alopecia. While this disease most commonly manifests in the muscle and skin, it is a multisystem disorder that may involve the joints, gastrointestinal tract, lungs, and/or heart.1

See also pages 70, 109, and 113

Systemic corticosteroid treatment remains the mainstay of therapy despite its associated adverse effects and is usually begun at a daily dose equivalent to 0.5 to 1.0 mg/kg of prednisone. Steroid-related toxic effects may be prevented by early intervention with an immunosuppressive or cytotoxic agent such as methotrexate sodium,2,3 azathioprine sodium,1 cyclophosphamide,1 chlorambucil,1 cyclosporine,1 or mycophenolate mofetil.5,6 Some patients with cutaneous lesions have shown a response to antimalarial agents.7,8 The only published double-blind, placebo-controlled trial9 demonstrated that treatment with intravenous immunoglobulin led to significant improvement in patients with recalcitrant DM for muscle as well as skin disease. Combination immunosuppressive therapies or total body irradiation may also be useful in patients unresponsive to therapy.1 Controlling skin manifestations may be more difficult than treating the myositis, and cutaneous symptoms often persist despite treatment with corticosteroids and/or immunosuppressive agents.10

Herein, we report our experience with the use of mycophenolate mofetil in patients with DM for whom conventional therapies failed and/or caused toxic effects.

METHODS

We retrospectively analyzed our open-label observations of 12 patients (11 women and 1 man) with classic features of DM. All records of patients who had been diagnosed with DM were reviewed. Inclusion criteria included a characteristic clinical rash as well as a skin biopsy finding compatible with DM, laboratory or clinical evidence of muscle disease, and a lack of response to antimalarial agents.10 The only published double-blind, placebo-controlled trial9 demonstrated that treatment with intravenous immunoglobulin led to significant improvement in patients with recalcitrant DM for muscle as well as skin disease. Combination immunosuppressive therapies or total body irradiation may also be useful in patients unresponsive to therapy.1 Controlling skin manifestations may be more difficult than treating the myositis, and cutaneous symptoms often persist despite treatment with corticosteroids and/or immunosuppressive agents.10

Herein, we report our experience with the use of mycophenolate mofetil in patients with DM for whom conventional therapies failed and/or caused toxic effects.

Author Affiliations: Division of Dermatology, Department of Medicine, University of Louisville School of Medicine, Louisville, Ky.
developed a leukopenia, elevated liver enzyme and serum aldolase levels, and symptoms of urinary frequency while undergoing mycophenolate mofetil monotherapy. Cessation of mycophenolate mofetil treatment with simultaneous institution of chlorambucil therapy resulted in resolution of both the laboratory abnormalities and urinary symptoms.

Patient 5 developed an Epstein-Barr virus–related B-cell lymphoma of the central nervous system while undergoing treatment with methotrexate sodium at 35 mg/wk and mycophenolate mofetil at 1.5 g twice a day. (This patient was the subject of a previous case report.13) These drug treatments were discontinued, and the patient improved without further intervention over the next 2 months. Patient 5 is no longer being treated with mycophenolate mofetil. This patient is now being treated with prednisone at 15 mg every other day and pimecrolimus cream.

Two patients experienced a mild leukopenia, and 1 of them also had a concurrent thrombocytopenia. Neither of these hematologic abnormalities required a dose adjustment in the medication. Another patient noted feeling weak, tired, and fatigued with occasional nausea. This gradually improved over the course of therapy and did not result in a discontinuation of treatment. Five patients were successfully maintained on mycophenolate mofetil monotherapy for several months at doses ranging from 0.5 to 3 g/d. Mycophenolate mofetil therapy for the other patients was maintained at doses of 2 to 3 g/d in addition to other agents such as methotrexate or prednisone. In these patients, the doses of other immunosuppressive agents were lowered from their initial levels with the addition of mycophenolate mofetil to the regimen.

The treatment of idiopathic inflammatory myopathies can be challenging. Oral corticosteroids are generally considered the primary therapy for DM; however, they are not effective in all patients and are frequently associated with adverse effects. It is imperative that the clinician weigh the potential benefit against the risks for each patient. In an attempt to prevent the occurrence of adverse effects, several corticosteroid-sparing agents, including antimalarials, methotrexate, azathioprine, chlorambucil, cyclosporine, and cyclophosphamide, have been used in combination with low-dose steroids or as an alternative treatment with varying degrees of success. Intravenous immunoglobulin infusions have also been useful in some patients unresponsive to standard treatment.9

There have been no double-blind, placebo-controlled trials demonstrating superiority of one agent over another, so the choice of immunosuppressive agent must take into consideration the comorbidities in the individual patient as well as the potential adverse effects of the agent to be chosen.12 Many of the problems associated with conventional therapies relate to their end-organ toxic effects. Therapy with mycophenolate mofetil has not been shown to demonstrate any significant end-organ toxic effects, so it may prove to be a viable alternative in those patients whose comorbid conditions preclude the use of more traditional therapies.
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<th>Patient No./ Sex/ Age, y</th>
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Abbreviations: bid, twice a day; CNS, central nervous system; GI, gastrointestinal; LFT, liver function test; qd, once daily; qhs, every night; qod, every other day.

*Mycophenolate mofetil treatment stopped owing to the development of leukopenia, elevated serum aldolase and liver enzyme levels, and symptoms of urinary frequency.

†All treatment with immunosuppressive agents discontinued owing to development of CNS lymphoma.
A review of the mechanism of action and potential adverse effect profile can be found in the review by Kitchin et al. In summary, mycophenolate mofetil is a semisynthetic 2-morpholinoethyl ester of mycophenolic acid. It is available for oral administration and displays superiority in both bioavailability and activity over its parent compound, mycophenolic acid. Once ingested, mycophenolate mofetil is hydrolyzed to mycophenolic acid, the active form of the drug, which selectively inhibits inosine monophosphate dehydrogenase in eukaryotic cells. This in turn inhibits de novo purine biosynthesis by blocking the conversion of inosine-5-phosphate and xanthine-5-phosphate to guanosine-5-phosphate, ultimately resulting in inhibition of the proliferative responses of B and T lymphocytes lacking the salvage pathway, inhibition of antibody formation, and prevention of the generation of cytotoxic T cells. Mycophenolate mofetil is metabolized by the liver and excreted by the kidneys. However, unlike other immunosuppressive agents, it displays no significant hepatotoxic or nephrotoxic effects. In addition to its immunosuppressive action, mycophenolic acid also possesses antifungal, antibacterial, and antiviral properties in vitro. There have been reports of successful use of mycophenolate mofetil in the treatment of pemphigus vulgaris, paraneoplastic pemphigus, bullous pemphigoid, pemphigus foliaceus, pyoderma gangrenosum, severe refractory atopic dermatitis, perineal and metastatic cutaneous Crohn disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, sarcoid, and DM.

Our patients tolerated therapy with mycophenolate mofetil well. We recognize that these observations are limited by our study’s retrospective and noncontrolled nature and relative lack of objective measurements. Nonetheless, we observed only 2 toxic reactions requiring cessation of therapy: one was in a patient taking concomitant methotrexate and low-dose oral corticosteroids, and the other occurred in a patient undergoing mycophenolate mofetil monotherapy. In general, the most commonly reported adverse effects are gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain, dyspepsia, and gastroenteritis). Less commonly, patients experience genitourinary symptoms, hematologic abnormalities (leukopenia, anemia-thrombocytopenia, and pancytopenia), and neurologic symptoms (weakness, tiredness, headache, tinnitus, and difficulty sleeping).

Several studies of transplant recipients being treated with mycophenolate mofetil suggest an increased risk of opportunistic infections while taking this medication, including herpes simplex, Candida, atypical Mycobacteria species, cytomegalovirus viremia syndrome, and invasive cytomegalovirus disease. Others have argued that the increased incidence could be attributed to the concomitant use of additional immunosuppressive agents. Herein, we report a case of Epstein-Barr virus–related methotrexate-associated lymphoma of the central nervous system; however, studies of mycophenolate mofetil monotherapy have demonstrated no increased risk. Although these adverse effects are observed at doses of 2 g/d, they are more commonly seen at 3 g/d and rarely necessitate discontinuation of treatment. There are no well-established guidelines for monitoring patients. It is generally recommended that clinicians carefully monitor the complete blood cell count while the patient is undergoing therapy.

In conclusion, it is our experience that patients with DM generally tolerate doses of mycophenolate mofetil up to 3 g/d with minimal adverse effects. Some of the patients in our series continued treatment with other agents such as prednisone and methotrexate in addition to mycophenolate mofetil. These patients were weaned from these other agents as their disease began to improve. Ten of the 12 patients in this series demonstrated significant improvement within 8 weeks of initiating mycophenolate mofetil therapy. The development of a central nervous system lymphoma in 1 patient undergoing concomitant immunosuppressive therapy as well as the development of a breast cancer in a patient with a re-
mote history of breast cancer in the contralateral breast emphasizes the need for vigilant surveillance for opportunistic infections and malignancies in all patients treated with immunosuppressive agents. We propose that mycophenolate mofetil be added to the list of effective therapies for patients with DM.

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Correspondence: Jeffrey P. Callen, MD, 310 E Broadway, Louisville, KY 40202 (jefca@aol.com).

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REFERENCES


News and Notes

20th Continuing Medical Education Course for Practical Dermatology and Venereology. Munich, Germany, July 23 to 28, 2006. Lectures will be held in German. Information and registration: Prof Dr Gerd Plevig (Congress President), Priv-Doz Dr Peter Thomas (Organizing Committee), Mrs Gertrud Hammel (Congress Office). Address: Fortbildungswwoche für praktische Dermatologie und Venereologie e.V. c/o Department of Dermatology, Ludwig-Maximilians-University Munich, Frauenlobstrasse 9-11, D-80337 Munich, Germany; telephone, 49-89-5160 6065; fax, 49-89-5160 6066; www.fortbildungswwoche.de. Registration will start in November 2005.