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 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

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,3 cyclophosphamide,1 chlorambucil,1 cyclosporine,1 or mycophenolate mofetil.3,6 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 or history of toxic effects from conventional therapies. Patients were excluded if they were pregnant or lactating, had an active malignancy, or were treated with mycophenolate mofetil for less than 1 month. Collected data included the patient’s age at the time of record, age at diagnosis, sex, previous therapies, reasons for discontinuation of therapies, dose of mycophenolate mofetil, response to mycophenolate mofetil, time to response with mycophenolate mofetil, and current treatment regimen.

All patients were instructed to apply a broad spectrum, high sun protection factor sunscreen daily, and those with symptomatic muscle disease were instructed to limit their physical activity. Patients began oral mycophenolate mofetil treatment at doses ranging from 1 g/d in divided doses to 1 g twice a day and were generally maintained on their current therapy. In the absence of response and toxic effects, the dose of mycophenolate mofetil was increased to 2 to 3 g/d. When possible, all patients were examined monthly, and response evaluation was based on reported medical history (decrease in pruritus or burning and/or a decrease in the dose of other immunosuppressive medications), clinical examination (strength and/or degree of cutaneous involvement), and laboratory parameters including aldolase and serum creatine kinase enzyme levels.

### RESULTS

The Table summarizes the characteristics of these patients, including their previous therapies, reasons for discontinuation of these therapies, and their time to response with mycophenolate mofetil. Figure 1 shows patient 11 before mycophenolate mofetil treatment, and Figure 2 demonstrates her response after mycophenolate mofetil treatment.

All patients were adults (11 women and 1 man) ranging in age from 28 to 63 years (mean age, 48.5 years). For all patients, conventional therapies had failed and/or caused toxic effects requiring their discontinuation, as outlined in the Table. Response to treatment was defined as improvement in clinical symptoms and/or decreases in serum creatine kinase or aldolase levels. Ten of the 12 patients experienced improvement in both cutaneous and muscular symptoms within 4 to 8 weeks of initiating mycophenolate mofetil therapy. The initial dose of mycophenolate mofetil ranged from 1 g/d in divided doses to 1 g twice a day. All responders ultimately responded to 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.

### COMMENT

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 antimarials, 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.
<table>
<thead>
<tr>
<th>Patient No./ Age, y</th>
<th>Sex</th>
<th>Previous Therapy (Dose), Reason for Discontinuation</th>
<th>Mycophenolate Mofetil Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/63* 51</td>
<td>F</td>
<td>Prednisone (10 mg qd), poor control</td>
<td>Initial Dose, g bid</td>
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<tr>
<td></td>
<td></td>
<td>Dapsone (100 mg qd), poor control</td>
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<tr>
<td></td>
<td></td>
<td>Methotrexate sodium (30 mg/wk), abnormal liver biopsy finding</td>
<td>Hydroxychloroquine sulfate (200 mg bid), drug eruption</td>
</tr>
<tr>
<td>2/F/51 41</td>
<td>F</td>
<td>Hydroxychloroquine sulfate (200 mg bid), poor control</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate sodium (12.5 mg/wk), poor control Chlorambucil (2 mg qd), poor control</td>
<td></td>
</tr>
<tr>
<td>3/F/32 18</td>
<td>F</td>
<td>Prednisone (10 mg qd), poor control</td>
<td>Initial Dose, g bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydroxychloroquine sulfate (200 mg bid), poor control Chloroquine phosphate (250 mg bid), poor control Quinacrine hydrochloride (100 mg qd), poor control Methotrexate sodium (20 mg/wk), poor control Azathioprine (100 mg qd), poor control Intravenous immunoglobulin (1 g/kg per day on 2 consecutive days/mo), poor control</td>
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<tr>
<td>4/F/63 60</td>
<td>F</td>
<td>Prednisone (40 mg qd), flares on tapering Methotrexate sodium (30 mg/wk), anemia</td>
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<td></td>
<td>Methotrexate sodium (35 mg/wk), thrombocytopenia Prednisone (30 mg qd), no reason specified Hydroxychloroquine sulfate (200 mg bid), drug eruption Thalidomide (200 mg qhs), poor control</td>
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</tr>
<tr>
<td>5/F/46† 40</td>
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<td>Methotrexate sodium (10 mg/wk), nausea</td>
<td>Initial Dose, g bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisone (30 mg qd), flares on tapering Hydroxychloroquine sulfate (200 mg bid), drug eruption Chlorambucil (2 mg qd)</td>
<td></td>
</tr>
<tr>
<td>6/F/34 30</td>
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<td>Methotrexate sodium (15 mg/wk), increased levels on LFT Hydroxychloroquine sulfate (200 mg bid), drug eruption Chloroquine phosphate (250 mg bid), retinopathy</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate sodium (30 mg/wk), no reason specified Hydroxychloroquine sulfate (200 mg bid), drug eruption Thalidomide (200 mg qhs), poor control</td>
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<tr>
<td>7/F/47 44</td>
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<td>Stevens-Johnson syndrome</td>
<td>Initial Dose, g bid</td>
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<td></td>
<td>Methotrexate sodium (30 mg/wk), poor control Chlorambucil (2 mg qd)</td>
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</tr>
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<td>8/F/41 36</td>
<td>F</td>
<td>Methotrexate sodium (15 mg/wk), increased levels on LFT Hydroxychloroquine sulfate (200 mg bid), drug eruption Chloroquine phosphate (250 mg bid), retinopathy</td>
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<tr>
<td></td>
<td></td>
<td>Methotrexate sodium (30 mg/wk), no reason specified Hydroxychloroquine sulfate (200 mg bid), drug eruption Thalidomide (200 mg qhs), poor control</td>
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<tr>
<td>9/M/62 56</td>
<td>M</td>
<td>Prednisone (60 mg qd), poor control</td>
<td>Initial Dose, g bid</td>
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<td>Methotrexate sodium (50 mg qd), poor control and increased levels on LFT Chlorambucil (2 mg qd)</td>
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</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>11/F/59 58</td>
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<td>Prednisone (20 mg qd), elevated glucose level and cushingoid appearance Methotrexate sodium (17.5 mg/wk), GI disturbances, acute necrotizing erosive gingivitis</td>
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<tr>
<td></td>
<td></td>
<td>Methotrexate sodium (17.5 mg/wk), GI disturbances, acute necrotizing erosive gingivitis</td>
<td></td>
</tr>
<tr>
<td>12/F/32 28</td>
<td>F</td>
<td>Hydroxychloroquine sulfate (200 mg bid), poor control Prednisone (60 mg qd), poor control Methotrexate sodium (40 mg/wk), poor control</td>
<td>Initial Dose, g bid</td>
</tr>
</tbody>
</table>

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 Kit-chin et al.\textsuperscript{13} 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 path-

way, 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 foliaceous, pyoderma gangrenosum, severe refractory atopic dermatitis, perineal and metastatic cutaneous Crohn disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, sarcoid, and DM.\textsuperscript{13-24}

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 mycopheno-
late mofetil monotherapy. In general, the most commonly reported adverse effects are gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain, dyspepsia, and gastroenteritis).\textsuperscript{13} Less commonly, patients experience genitourinary symptoms, hematologic abnormalities (leuko-
penia, anemia-thrombocytopenia, and pancytopenia), and neurologic symptoms (weakness, tiredness, headache, tinnitus, and difficulty sleeping).\textsuperscript{13}

Several studies of transplant recipients\textsuperscript{24-26} 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 cy-
tomegalovirus disease. Others have argued that the increased incidence could be attributed to the concomitant use of ad-
tional immunosuppressive agents. Herein, we report a case of Epstein-Barr virus–related methotrexate-assoc-
ated lymphoma of the central nervous system; however, studies of mycophenolate mofetil monotherapy have demonstrated no increased risk.\textsuperscript{27} Although these adverse effects are observed at doses of 2 g/d, they are more com-
monly seen at 3 g/d and rarely necessitate discontinuation of treatment.\textsuperscript{13} 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.\textsuperscript{27}

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 pa-
tients in our series continued treatment with other agents such as prednisone and methotrexate in addition to my-
cophenolate 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 mycopheno-
late mofetil therapy. The development of a central ner-
vous system lymphoma in 1 patient undergoing con-
comitant 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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REFERENCES


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 Plewig (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 6063; fax, 49-89-5160 6066; www.fortbildungwoche.de. Registration will start in November 2005.