Treatment of Pemphigus Vulgaris and Pemphigus Foliaceus With Mycophenolate Mofetil

Daniel Mimouni, MD; Grant J. Anhalt, MD; Deborah L. Cummins, BS; David J. Kouba, MD, PhD; Jennifer E. Thorne, MD; H. Carlos Nousari, MD

Background: Mycophenolate mofetil is increasingly being used as a corticosteroid-sparing agent in immunosuppressive regimens.

Objective: To elucidate the effectiveness of mycophenolate as adjuvant therapy in the treatment of both pemphigus vulgaris and pemphigus foliaceus.

Design: Historical prospective study.

Setting: University hospital.

Patients: The study included 42 consecutive patients with pemphigus (31 with pemphigus vulgaris and 11 with pemphigus foliaceus) who had relapses during prednisone taper or had clinically significant adverse effects from previous drug therapy.

Results: Remission was achieved in 22 (71%) and 5 (45%) of patients with pemphigus vulgaris and pemphigus foliaceus, respectively. Partial remission was achieved in 1 (3%) and 4 (36%), respectively. The median time to achieve complete remission was 9 months (range, 1-13 months). The treatment was administered for a median of 22 months, and the median follow-up period was 22 months. Seventy-seven percent of patients had no adverse effect. Two patients had side effects severe enough to necessitate discontinuation of treatment, one because of symptomatic but reversible neutropenia and the other because of nausea.

Conclusion: Mycophenolate is an effective and safe adjuvant in the treatment of both pemphigus vulgaris and pemphigus foliaceus.

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direct immunofluorescence with IgG as the dominant immunoreactant with or without C3 deposition on epithelial cell surfaces and without any staining at the basement membrane zone; (4) circulating IgG antiepithelial antibodies binding epithelial cell surfaces without recognizing the basement membrane zone, as demonstrated by (a) indirect immunofluorescence with monkey esophagus used as a substrate or (b) antidesmoglein IgG antibodies by enzyme-linked immunosorbent assay; and (5) absence of circulating IgG antibodies binding epithelial cell surface of murine bladder epithelium. Other inclusion criteria were at least 3 months of treatment with a minimum mycophenolate mofetil dosage of 35 mg/kg per day and a minimum follow-up period of 6 months after initiation of mycophenolate therapy. Dosing regimens were based on ideal (lean) body weight and not actual weight. Paraneoplastic pemphigus was excluded on the basis of clinical grounds as well as negative immunopathologic and serologic findings.

Any previous treatment, excluding prednisone, was discontinued before mycophenolate treatment was started. Statistical analysis to compare rates of remissions or failures in the different groups was performed with the $\chi^2$ test.

**FOLLOW-UP**

Remission was defined by the absence of lesions for a minimum of 4 weeks, while being treated with mycophenolate and a prednisone dosage of less than or equal to 0.15 mg/kg per day (7.5-12.5 mg/d or 20 mg every other day). Partial remission was defined as the presence of 1 to 5 cutaneous or mucous membrane lesions lasting more than a week in a patient treated with mycophenolate and a prednisone dosage less than or equal to 0.15 mg/kg per day (7.5-12.5 mg/d or 20 mg every other day). Failure was defined as a failure to meet criteria for partial remission or remission, or relapse subsequent to remission while still undergoing combination therapy. No other adjuvant was used during the time of the study, unless the patient’s treatment was defined as a failure. Mycophenolate was discontinued in the failure group.

Patients were initially treated on a monthly basis; on consideration of clinical grounds as well as negative immunopathologic and serologic findings.

Patients were initially treated on a monthly basis; on completion of clinical remission, patients were followed up every 6 months. Complete blood cell count and a comprehensive metabolic panel including aminotransferases, bilirubin, glucose, alkaline phosphatase, creatinine, and serum urea nitrogen were performed monthly.

Autoantibodies titers were performed at baseline and after entering remission or relapse by indirect immunofluorescence on monkey esophagus and antidesmoglein 3 and 1 enzyme-linked immunosorbent assay in all patients and 10 patients, respectively.

**STATISTICAL ANALYSIS**

Time to remission in patients treated with mycophenolate was calculated by means of Kaplan-Meier techniques performed with the Intercooled Stata 7.0 statistical software program (Stata Corp., College Station, Tex).11 Those patients not observed to have remission of their disease while being treated with mycophenolate, whether because of death, loss to follow-up, or end of the study, were censored at the time they were last known to be alive and without remission during mycophenolate treatment. Comparisons of times to remission between patients with PV and those with PV were tested by log-rank and Wilcoxon rank-sum tests.12

**RESULTS**

Forty-two patients with clinical and immunopathologically confirmed pemphigus (31 patients with PV and 11 patients with PF) were included. On diagnosis, the patients were immediately treated with prednisone at a dosage of 1 mg/kg per day, and any other adjuvant treatment was discontinued and not allowed during the study period, unless the patient’s treatment was considered a failure. Prednisone dose was gradually tapered, and if the patient’s disease flared significantly, the dose was temporarily held stable (but not increased) while mycophenolate treatment was initiated.

Mycophenolate was added in 31 patients because of relapses that occurred during prednisone tapering (these patients were treated with prednisone as a single agent). In this group, 10 patients were at a prednisone dosage of less than 0.5 mg/kg per day, and 21 patients were at a prednisone dosage of 0.5 to 1 mg/kg per day. In an additional 11 patients, mycophenolate was added because of intolerance to azathioprine, manifested by severe gastrointestinal symptoms, elevated aminotransferase levels, and/or severe cytopenia. In this group, 3 patients were at a prednisone dosage of less than 0.5 mg/kg per day, and 8 patients were at a prednisone dosage of 0.5 to 1 mg/kg per day.

Remission was achieved in 22 (71%) and 5 (45%) patients of PV and PF, respectively. Partial remission was achieved in 1 (3%) and 4 (36%), respectively (Table 1). As an adjuvant, mycophenolate failed to control the disease in 10 patients (24%). Differences in the response to mycophenolate between PV and PF were not statistically significant.

An initial favorable response was not sustainable in 2 patients with PV who had initially achieved remission. These patients had relapses after remissions lasting 9 months in one patient and 15 months in the second. These 2 subjects were included in the failure group, as defined by the aforementioned criteria.

The median time to achieve remission was 9 months (range, 1-13 months). Mycophenolate was administered in the patients for a median of 22 months, and the

<table>
<thead>
<tr>
<th>Pemphigus Variant</th>
<th>Treatment Failure</th>
<th>Partial Remission</th>
<th>Remission</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>8 (26)†</td>
<td>1 (3)</td>
<td>22 (71)</td>
<td>31 (100)</td>
</tr>
<tr>
<td>PF</td>
<td>2 (18)</td>
<td>4 (36)</td>
<td>5 (45)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Total</td>
<td><strong>10</strong></td>
<td><strong>5 (12)</strong></td>
<td><strong>27 (64)</strong></td>
<td><strong>42 (100)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: PF, pemphigus foliaceus; PV, pemphigus vulgaris.

*Percentages have been rounded and may not total 100.
†Two of the 8 patients with treatment failure achieved remission but subsequently relapsed during treatment.
median follow-up period from treatment initiation was 22 months (Table 2). The cumulative probability of having a complete remission was 76% at 2 years of follow-up (Figure).

Patient demographics are detailed in Table 3. No statistically significant differences in response or failure were found on the basis of characteristics such as age, sex, and ethnicity (data not shown).

With respect to safety, all patients tolerated mycophenolate very well and 77% had no adverse effects. The most prevalent adverse effect involved gastrointestinal complaints, observed in 8 (19%) of patients (Table 4). The most frequent of these were nonspecific abdominal discomfort and mild diarrhea, which, in most patients, was transient and did not necessitate dosage adjustment. In 1 patient, mycophenolate mofetil dosage was reduced from 45 to 30 mg/kg per day, with resolution of symptoms, and 1 patient discontinued treatment after 8 months because of nausea but sustained a lasting remission. In addition, 1 patient had 2 episodes of symptomatic but reversible neutropenia, requiring antibiotic treatment.

There was no clinically significant elevation in results of liver function tests. No clinically significant infections (including herpes zoster) were reported in these patients, and no neoplasm developed during the follow-up period.

There were no statistical differences in the incidence of adverse effects between PV and PF, or between patients who had achieved complete and/or partial remission, or between different demographic populations. A good correlation between autoantibody titers by indirect immunofluorescence and enzyme-linked immunosorbent assay and disease activity was observed, with a rapid decrease in titer in responding patients (data not shown).

The introduction of corticosteroids for the treatment of pemphigus has changed this previously lethal disease into a treatable one. However, significant morbidities and even mortality still occur, primarily because of the adverse effects of long-term corticosteroid therapy.

The benefits of adjuvant immunosuppressive therapies have been attributed to their corticosteroid-sparing properties, rather than greater immunosuppressive effects. Hence, a significant decrease in corticosteroid-related toxic effects has been observed. Among these drugs, antimetabolites and alkylating agents have consistently produced effective and durable therapeutic effects.

The most commonly used agents in these groups are azathioprine and cyclophosphamide. The side effect profiles of these agents differ from that of corticosteroids. However, potentially very serious adverse events are not uncommonly encountered at dosages proven to be effective in treating pemphigus. Moreover, idiosyncratic adverse effects such as azathioprine-induced hypersensitivity can be fatal.

Mycophenolate is an antimetabolite that selectively inhibits inosine monophosphate dehydrogenase, a key enzyme in the de novo synthesis of purines and a critical step in lymphocyte proliferation. Since Food and Drug Administration approval for prevention of renal transplant rejection, the effectiveness and safety profile of mycophenolate have sparked rapidly expanding interest.

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### Table 2. Treatment Periods and Follow-up of Patients With Remission and Partial Remission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Time, mo, Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment period to achieve remission</td>
<td>9 (1-13)</td>
</tr>
<tr>
<td>Treatment period with mycophenolate mofetil</td>
<td>22 (6-49)</td>
</tr>
<tr>
<td>Follow-up treatment period</td>
<td>22 (6-49)</td>
</tr>
</tbody>
</table>

### Table 3. Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>42</td>
</tr>
<tr>
<td>Pemphigus variant, No. (%)</td>
<td>31 (74)</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>1 (21/21)</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>1 (21:21)</td>
</tr>
<tr>
<td>Age at diagnosis, median (range), y</td>
<td>47.2 (6-74)</td>
</tr>
<tr>
<td>Ethnicity, No. (%)*</td>
<td></td>
</tr>
<tr>
<td>Jewish</td>
<td>22 (52)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (10)</td>
</tr>
<tr>
<td>African American</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Arabic</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Eastern European (non-Jewish)</td>
<td>7 (17)</td>
</tr>
</tbody>
</table>

*Percentages have been rounded and may not total 100.

### Table 4. Adverse Effects of Mycophenolate Mofetil

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal symptoms†</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Cytopenia‡</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1 (2)</td>
</tr>
<tr>
<td>None</td>
<td>32 (76)</td>
</tr>
<tr>
<td>Total</td>
<td>42 (100)</td>
</tr>
</tbody>
</table>

*Percentages have been rounded and may not total 100.

†Mainly mild abdominal discomfort and nausea that was short lived and did not necessitate dose adjustment. One patient discontinued mycophenolate mofetil after 8 months because of intolerance of the nausea.

‡Febrile neutropenia.
off-label use in immune-mediated diseases, including autoimmune and inflammatory skin disorders.10,14,15

Mycophenolate has recently been used in the treatment of PV. In a small number of patients, mycophenolate has proved to be safe and at least as effective as azathioprine; however, in this study, patients were treated with high dosages of corticosteroids concurrently with the administration of mycophenolate.8,9

We have used mycophenolate extensively in patients with pemphigus examined in the Division of Dermatoimmunology since early 1998.

To our knowledge, this is the largest case series of PV and PF treated with this agent. Medical records of 42 patients with nonparaneoplastic pemphigus treated with mycophenolate were analyzed. All patients received prednisone at the same starting dosage and had an initial clinical response. Mycophenolate was initiated at the same dosage in each patient after either inability to taper prednisone or intolerance to azathioprine. Mycophenolate was used for a median of 22 months.

Although the recommended dosage of mycophenolate for renal transplant recipients is 30 mg/kg per day, according to recent observations, dermatologic diseases may require dosages from 35 to 45 mg/kg per day. The higher dosages required in dermatology are likely related to the use of mycophenolate as a single adjuvant, as opposed to posttransplantation use, in which patients take mycophenolate in combination with synergistic immunosuppressive agents such as cyclosporine or tacrolimus. These agents augment the effectiveness of mycophenolate but also dramatically increase the incidence of dangerous adverse effects, thus precluding their use in pemphigus. In dermatologic disorders, mycophenolate is usually used in combination only with corticosteroids, hence the lower incidence of immunosuppression-related adverse effects and the need for higher dosages.10,16,17

In our study, most patients had a rapid clinical response, were able to taper their prednisone, and achieved remission (as defined by this study) at a median of 9 months. In 10 patients (24%), treatment was considered a failure and mycophenolate was discontinued (Table 1). We found no statistically significant difference in the clinical response between patients with PV and PF and no difference in varying ethnicities or sex.

There was 1 pediatric patient (aged 6 years) included in the study, and in this patient mycophenolate treatment failed. Interestingly, this patient's condition subsequently failed to respond to azathioprine but did respond to cyclophosphamide (data not shown).

As previously reported in the literature, mycophenolate was well tolerated and most patients reported no adverse effects. The most common adverse effect was mild gastrointestinal distress, and, with the exception of 1 patient who discontinued mycophenolate after 9 months and 1 patient whose dosage required lowering, most patients tolerated these symptoms without dosage modification. Interestingly, the same patient who discontinued mycophenolate because of gastrointestinal distress had previously discontinued azathioprine because of hepatotoxicity. No clinically significant elevation of results of liver function tests was observed during mycophenolate treatment in any patient. Follow-up was conducted for a median duration of 22 months, with a maximum of 49 months.

This study demonstrated that mycophenolate is an effective and safe adjuvant in the treatment of patients with PV or PF whose prednisone dosage could not be adequately tapered or in whom azathioprine as a corticosteroid-sparing agent had previously failed. In contrast to azathioprine, the adverse effects of mycophenolate appear to be dose dependent and rarely clinically significant. Mycophenolate is approximately 4 times more expensive than azathioprine. However, the need for more frequent routine laboratory monitoring, thiopurine methyl transferase screening, and potentially more frequent management of adverse effects in azathioprine-treated patients may warrant the use of mycophenolate as first-line adjuvant therapy.

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REFERENCES