Article type : Review

Mycophenolate Mofetil as Adjunctive Therapy to Corticosteroids for the Treatment of Pyoderma Gangrenosum: A Case Series and Literature Review

Matthew L. Hrin, BA; Arjun M. Bashyam, BA; William W. Huang, MD, MPH, Steven R. Feldman, MD, PhD

1 Center for Dermatology Research, Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, North Carolina
2 Department of Pathology, Wake Forest School of Medicine, Winston-Salem, North Carolina
3 Department of Social Sciences & Health Policy, Wake Forest School of Medicine, Winston-Salem, North Carolina
4 Department of Dermatology, University of Southern Denmark, Odense, Denmark

Address correspondence to:
Matthew L. Hrin, BA
Department of Dermatology, Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1071

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Pyoderma gangrenosum is a rare neutrophilic dermatosis that is commonly treated with systemic corticosteroids; however, their potent side effects may warrant tapering, and non-steroidal systemic immunosuppressants may help maintain or bolster disease clearance during weaning. Although cyclosporine is regarded as a favorable steroid-sparing agent, it is associated with several side effects, such as renal toxicity and hypertension, that may limit its feasibility. Mycophenolate mofetil is a well-tolerated alternative with limited data.
Mycophenolate Mofetil for Pyoderma Gangrenosum

Institutional review board approval was obtained to review patients from a single institution who received mycophenolate mofetil for pyoderma gangrenosum between January 1, 2010 – December 31, 2019. A systematic MEDLINE (PubMed) review was performed of articles containing linked keywords: “mycophenolate mofetil” and “pyoderma gangrenosum”. Patient demographics, presentation details, and treatment regimen characteristics were recorded.

Fourteen of our pyoderma gangrenosum patients were treated with mycophenolate mofetil concomitantly with prednisone. Ninety-three percent of our patients achieved improvement within 12 months (mean 4.5 months), including five patients who experienced complete healing. Outcomes in literature patients were comparable; 77% either improved or maintained clearance with mycophenolate mofetil. Greater than 80% of total patients experienced healing or adequate disease control at a median dose of 2000 mg daily. The most common side effects of mycophenolate mofetil were myelosuppression and gastrointestinal upset, which were both seen in 18% of patients.

Although this study is subject to publication bias, mycophenolate mofetil appears to be an efficacious and well-tolerated adjunctive therapy option for pyoderma gangrenosum.

Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that affects roughly 3 to 10 patients per million people per year.¹ There are various forms of PG which have distinctive clinical features; the main variants include: ulcerative (classical) PG (tender ulcerations with purulent and necrotic bases), peristomal PG (ulcerations in the peristomal area), bullous PG (inflammatory bullae which erode to form superficial ulcers), and pustular PG (tender pustules with surrounding erythema).¹ While topical corticosteroids (TCSs) or topical calcineurin inhibitors (TCIs) are first-line treatments for mild cases, widespread or rapidly-progressive presentations generally require systemic therapy.² Systemic corticosteroids (SCSs) are frequently combined with adjunctive immunosuppressants during tapering or when SCSs are ineffective monotherapies.² Although popular, cyclosporine may not be effective and is associated with renal toxicity and hypertension.³ Mycophenolate mofetil (MMF) is a well-tolerated alternative with sparse PG data. Here, we present a 14-patient retrospective case series and a literature review of 24 studies treating 63 patients.
Methods

Upon institutional review board approval, patients from a single institution who received MMF for PG between January 1, 2010 – December 31, 2019 were identified. Patients lost to follow-up or without biopsy were excluded. Patient demographics (age, sex, race), presentation details (PG subtype, chronic conditions, body area affected, previously attempted medications), and MMF regimen characteristics (maximum daily dose, duration, concomitant medications, side effects experienced) were recorded. Afflicted areas of involvement were categorized into high-level anatomic groups; for instance, the “lower extremity” category included lesions that affected the thigh, pretibial region, calf, foot, etc. Associated chronic conditions relevant to management (e.g. diabetes) and presentation (e.g. inflammatory bowel disease) were recorded. Outcomes were classified into the following groups: complete healing (no evidence of erythematous, purulent pustules or ulcers), significant improvement (almost completely healed), mild improvement (less erythema, less exudate, less pain), and no improvement (absence of a clinical response). If one patient had multiple lesions with different outcomes (e.g. complete healing of one ulcer, significant improvement of another ulcer), their outcome was categorized based on the most superior outcome (e.g. complete healing).

A systematic MEDLINE (PubMed) review was performed of articles containing linked keywords: “mycophenolate mofetil” and “pyoderma gangrenosum”. Articles available in the English language that reported cases of PG treated with MMF were included. Data regarding patient demographics, presentation details, and MMF regimen characteristics were collected using the same methodology that was utilized in our case series patients. Patient outcomes were categorized according to each articles’ descriptions, when available (e.g. “regressed completely” was classified as “complete healing”, “dramatic improvement” and “rapid improvement in all aspects of illness” were classified as “significant improvement”, “maintained clinical response” was classified as “maintained clearance”, “failed” was categorized as “no improvement”). If studies stated an improvement was achieved but did not provide details regarding the extent of improvement, the outcomes were categorized as “unspecified improvement”. Similar to the data collection methodology used in our patients, if one patient had multiple lesions with different outcomes, their outcome was categorized based on the best
outcome. Studies without patient-level data and parameters with unspecified values were
excluded from statistical analysis but were included in the discussion.

Results

Fourteen patients, mostly Caucasian (71%), female (57%), with a mean age of 53 years (range
29-69 years), with ulcerative PG met inclusion criteria (Table 1). Two patients (14%) had
associated inflammatory bowel disease (IBD). Lesions most commonly affected the lower
extremities (71%), but also involved the upper extremities (14%), trunk (14%), neck (7%), and
genital area (7%), with lesions concomitantly affecting more than one region in 14% of patients.

MMF was initiated at daily doses ranging from 1000-2500 mg (median 2000 mg). One-hundred
percent of patients concomitantly received prednisone (mean maximum dose 35 mg, tapered
to mean minimum dose 9 mg), 93% of which were continuations of regimens started before
MMF. Other co-administered medications included: intra-lesional triamcinolone, adalimumab,
and TCSs (clobetasol, fluocinonide). One patient failed cyclosporine due to renal toxicity.

Biologics (infliximab, adalimumab, etanercept) were administered to two patients, who
discontinued due to side effects (infusion reaction, strokes, fatigue, pneumonia, shortness of
breath). Methotrexate (MTX) caused intolerable side effects in four patients (most commonly
nausea (50%)). One patient suffered low G6PD levels with dapsone. Azathioprine caused
nausea and vomiting in one patient. One patient was lost to follow-up.

Most patients achieved improvement with MMF (93%; 5 complete healing, 4 significant, 4 mild)
within 12 months; one patient did not improve (Table 1). Side effects were experienced in 50%
of patients, including: hematologic suppression (21%), gastrointestinal upset (21%), shortness
of breath (14%), edema (14%), neurological symptoms (tremor and paresthesia; 7%), and
herpes simplex virus (HSV) infection (7%). Three patients discontinued MMF due to side effects.

Forty-three patients, mostly female (58%) with a mean age of 52 years (range 13-83 years), with
ulcerative (77%) and peristomal (23%) PG were identified in the literature (Table 1). Eight
patients (19%) had IBD. Ulcers were reported on the lower extremities (61%), trunk (39%),
genitals (7%), and neck (4%), with lesions concomitantly affecting more than one region in 7%
of patients. MMF was administered at daily doses ranging from 500-4000 mg (median 2000
mg). SCSs were commonly co-administered (68%), usually as continuations of therapy initiated
before MMF (84%). Other therapies attempted prior to MMF therapy included: cyclosporine

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(52%), dapsone (31%), azathioprine (21%), thalidomide (14%), triamcinolone (14%),
cyclophosphamide (14%), methotrexate (10%), IVIG (10%), tacrolimus (7%), clobetasol (7%),
betamethasone (7%), fluocinonide (4%), infliximab (4%), colchicine (4%), and adalimumab (4%).
Most patients reported in the literature improved or maintained clearance (77%) with
adjunctive MMF therapy without side effects (72%) (Table 1). Side effects included: infection
(9% - including one HSV infection), low blood counts (7%), gastrointestinal upset (5%), fatigue
(2%), MI (2%), headaches (2%), palpitations (2%), suspected DVT (2%), and sigmoid colon
perforation (2%).

Discussion
PG is an immune-mediated condition which often requires multi-drug regimens for successful
management. PG ulcers tend to heal slowly, and SCSs may be unsustainable long-term
treatments due to their potent side effects. MMF is well-tolerated and may provide adequate
disease control during SCS weaning. MMF is recognized mainly for transplant rejection
prophylaxis, but it is an effective off-label option for several dermatologic conditions.
Numerous case reports have shown promising results of MMF for PG, particularly when used
concomitantly with SCSs.
In our series, 93% of patients achieved improvement within 12 months (mean 4.5 months),
including five patients who achieved remission - three of which were tapered off of
corticosteroids completely (Table 1). While several patients (77%) experienced improvement
with SCS monotherapy, 100% of patients who did not improve on SCS monotherapy achieved
improvement with addition of MMF. Side effects were experienced by 31% of patients who
underwent SCS monotherapy (cushingoid features, atrial fibrillation, sleep disturbance) and it
is unknown if SCS tapering mitigated their side effects. Comparable improvement rates (77%)
and times to achieve improvement (mean 5 months) with MMF were reported in the literature;
however, a higher proportion of our patients experienced adverse effects (50% vs 28%). PG-
associated conditions, such as: IBD (14% our study, 19% literature reports), inflammatory
arthritis (0% our study, 12% literature reports), and hematologic malignancy (0% our study, 2%
literature reports) were observed less than in general PG studies (41.0% IBD, 20.5%
inflammatory arthritis, 5.9% hematologic malignancy). Although all of our patients had
ulcerative PG, one literature patient with peristomal PG achieved disease control with
prednisone and concomitant MMF (3 mg and 1000 mg daily, respectively). Another peristomal PG literature patient experienced significant improvement within one month of starting MMF at 1000 mg daily; the patient’s ulcer healed after a total of three months on MMF.

Chronic conditions such as diabetes and hypertension may curtail the viability of long-term SCS therapy. These conditions affected our patients (43% type 2 diabetes mellitus (T2DM), 36% hypertension) more than in literature reports (2% T2DM, 5% hypertension) (Table 1). However, literature patients were more commonly affected by chronic conditions which frequently involve long-term steroid therapy, such as IBD (19% vs 14%) and inflammatory arthritis (12% vs 0%). When comorbidities hinder the feasibility of long-term, high-dose SCS regimens, adjunctive MMF may help facilitate PG healing and/or prevent relapse during tapering of SCSs. Cyclosporine is a first-line steroid-sparing alternative or adjunctive therapy used with SCSs for PG, but is associated with considerable side effects, such as hypertension and renal toxicity, that may preclude its use in certain patients. Indeed, our patients had higher proportions of pre-existing chronic hypertension (36% vs 5%) and lower proportions of cyclosporine treatment (7% vs 52%) than literature reports (Table 1). Reasons cited for cyclosporine treatment failure in the literature reports included intolerable side effects (33%) and poor results (27%). The largest case series of MMF for PG to-date reported findings which challenge the notion of cyclosporine being a first-line steroid-sparing therapy, citing “the high number of patients who took cyclosporine before MMF implies cyclosporine is either ineffective or problematic.” However, that study excluded patients who succeeded on cyclosporine monotherapy—a source of potential bias. Our patient who received cyclosporine failed for both worsening lesions and renal toxicity. One literature case reported an initial response to cyclosporine, but recurrence occurred and the relapse ulcer did not respond. A similar issue was experienced with dapsone.

Several other therapies are also often attempted as adjunctive steroid-sparing therapy. Intra-lesional triamcinolone may provide benefit and can sometimes be considered first-line for superficial, localized PG. Azathioprine caused severe nausea and vomiting in our patient, and 33% of patients who received azathioprine in the literature failed due to side effects.

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Cyclophosphamide carries risk for myelosuppression and has issues with post-treatment relapse, which were observed in a literature case.\textsuperscript{16,17} This study excluded patients who succeeded on thalidomide, which may be an effective treatment for recalcitrant PG.\textsuperscript{18} Biologics may be favorable treatment options if patients can tolerate and afford them. Encouraging results with infliximab were observed in a randomized double-blind control trial.\textsuperscript{19} However, it caused an infusion reaction in one of our patients and shortness of breath and angioedema in a literature patient.\textsuperscript{20,21} Other anti-TNF agents, adalimumab and etanercept, have been successful in case reports and small case series.\textsuperscript{22,23} Two of our patients failed adalimumab for side effects: stroke, fatigue, pneumonia, and shortness of breath. One literature patient achieved remission with adalimumab.\textsuperscript{24} Etanercept failed in our patient for unknown reasons, and was not used in the literature cases.

Methotrexate is a popular steroid-sparing immunosuppressant, but is associated with numerous side effects.\textsuperscript{25} Four of our patients discontinued methotrexate due to: shortness of breath, edema, nausea, vomiting, and chronic cough. MMF was well-tolerated in literature reports and although seven (50\%) of our patients complained of side effects, only three (21\%) patients discontinued MMF due to them.

An emerging concern with MMF is its association with HSV infections, which was observed in one of our patients.\textsuperscript{26} One patient in the literature suffered an HSV infection; his recalcitrant PG resolved upon treatment of his HSV.\textsuperscript{27} Therefore, it may be helpful to consider the possibility of HSV when evaluating resistant PG cases, particularly if the patient has undergone MMF therapy.\textsuperscript{27} Anemia is another side effect that is associated with MMF; one case in the literature resolved with dose reduction.\textsuperscript{21} Gastrointestinal upset is a common side effect, but one patient experienced alleviation of this by switching to mycophenolate sodium, a more tolerable alternative.\textsuperscript{4,28} Two mortalities were observed in the literature: one sigmoid colon perforation and one due to an unrelated cause.\textsuperscript{4,12} The sigmoid colon perforation was suffered in a patient with an extensive history of steroid treatment before MMF and had many co-morbidities, including diverticular disease.

Two studies in the literature did not provide patient-level details. One was a 26-patient case series published by a group who reported 14/26 patients in a separate study with patient-level
The remaining 12/26 patients were not included in our statistical analysis. The overall 26-patient series had similar patient characteristics: mostly female (54%) with a mean age 66.3 years, with biopsy-proven ulcerative (96%) and bullous (4%) PG. Ulcers were similarly most commonly observed on the lower limbs (92%). All of their patients concomitantly received prednisolone (mean 40 mg (range 15-80 mg) at MMF initiation); 58% received additional immunosuppressants (11 cyclosporine, 5 azathioprine, 4 infliximab, 3 IVIG).

The second study without patient-level details was a review of MMF use at a tertiary hospital which grouped their PG patients with sweet syndrome patients. Stronger efficacy results were observed in atopic dermatitis and immunobullous disease cases than neutrophilic dermatoses. The overall incidence of side effects observed (47%) was similar to our case series (50%) (Table 1).

**Conclusion**

This study has inherent limitations of a case series study; additionally, our literature review is limited by publication bias, variable concomitant medications, subjective outcome measures, and differing lesion locations and PG subtypes. However, the results of MMF used in conjunction with SCSs appears promising and further prospective studies are warranted to compare cyclosporine and MMF as adjunctive therapy.

**Acknowledgment:** There are no funding sources to acknowledge.

**Questions (answers provided after references)**

1. Which of the following are potential side effects associated with cyclosporine?
   a. Hypertension
   b. Nephrotoxicity
   c. Nausea and vomiting
   d. All of the above

2. There is growing concern that mycophenolate mofetil may be associated with which of the following viruses?
   a. Herpes simplex virus
   b. Varicella zoster virus
   c. Coronavirus
   d. None of the above

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3. True or false: pyoderma gangrenosum is often painless but progresses quickly.

4. True or false: pyoderma gangrenosum may be an extraintestinal manifestation of Crohn’s disease and ulcerative colitis.

5. Which of the following conditions, if any, are relative contraindications to corticosteroid treatment?
   a. Chronic hypertension
   b. Type 2 diabetes mellitus
   c. Tuberculosis
   d. All of the above

6. True or false: mycophenolate mofetil is a well-tolerated steroid-sparing immunosuppressant with good specificity for lymphocytes.

7. Which of the following condition(s) are considered neutrophilic dermatoses?
   a. Sweet syndrome
   b. Pyoderma gangrenosum
   c. Behçet’s syndrome
   d. All of the above

8. True or false: mycophenolate mofetil may be associated with the development of anemia.

9. True or false: pyoderma gangrenosum is generally regarded as a diagnosis of exclusion.

10. True or false: eruptions of pyoderma gangrenosum ulcers may be triggered by minor trauma, such as a bump or a needle stick injury.

References:

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Answers to questions

1) D

2) A

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3) F
4) True
5) D
6) True
7) D
8) True
9) True
10) True
Table 1. Overview of patient characteristics and MMF regimen: our study, literature review, combined cases

<table>
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<tr>
<th>Characteristic</th>
<th>This Study Value, No. (%) (N = 14)</th>
<th>Literature Review Value, No. (%) (N = 43)</th>
<th>Combined Cases Value, No. (%) (N = 57)</th>
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<tr>
<td>Mean (SD)</td>
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<td>51.9 (19.8)</td>
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<th>Clinical</th>
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Chronic conditions*

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<td>Atopic dermatitis</td>
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<td>Inflammatory arthritis</td>
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<td>Systemic lupus erythematosus</td>
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Body region affected*

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<tr>
<td>Trunk</td>
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<td>13</td>
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Previous treatments*

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<td>Methotrexate</td>
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<tr>
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<td>Max MMF dose, mg</td>
<td>Outcome**</td>
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<td>Mean</td>
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Adalimumab 2 1 3
Clobetasol 2 2 4
Azathioprine 1 6 7
Cyclosporin 1 15 16
Dapsone 1 9 10
Etanercept 1 0 1
Infliximab 1 1 2
IVIG 1 3 4
Cyclophosphamide, Intralesional triamcinolone injection, methylprednisolone, prednisolone, thalidomide
Betamethasone, Tacrolimus 0 2 2
Colchicine 0 1 1

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<td>10 (23.2)</td>
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Adjunctive medications*

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</tr>
<tr>
<td>Fluocinonide</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intra-lesional triamcinolone</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Thalidomide, IVIG</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Side effects*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Before MMF</th>
<th>During MMF</th>
<th>Post-MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic suppression</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal upset (nausea, diarrhea)</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Edema</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
Herpes simplex virus infection  1  2  3
Other infection (pneumonia,  0  3  3
sepsis, septic arthritis)
Fatigue  0  2  2

* Patients may fall into more than one category
** If patient had multiple lesions, they were categorized based on the better outcome

1 All 14 unspecified PG types came from Li et al.’s review of MMF use in dermatology. In a separate article by Li et al., 26 PG patients were identified which included these 14 patients; 25/26 were ulcerative and 1 was bullous

2 If improvement was observed upon addition of another medication while on MMF, the outcome was categorized according to the improvement observed. If it was explicitly stated that MMF played a minimal role in improvement upon addition of other medications, the outcome was categorized as “no improvement”

Table legend
Table 1. High-level summary of patient presentation characteristics and details regarding their MMF regimen for patients included in our study, our literature review, and all cases combined