Treatment of pyoderma gangrenosum with mycophenolate mofetil as a steroid-sparing agent

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Background: Mycophenolate mofetil (MMF) has enjoyed increasing popularity as an emerging immunosuppressant treatment for various autoimmune dermatologic conditions, including pyoderma gangrenosum (PG).

Objective: The aim of this study was to examine the efficacy and safety of MMF as used in PG.

Methods: A retrospective chart review was conducted for all patients with PG treated with MMF at our institution (Victoria, Australia) for the past 11 years (2001-2012).

Results: We identified 26 patients, 14 female and 12 male. Nine patients (34.6%) had associated systemic conditions. All patients received prednisolone. MMF was used as a first-line steroid-sparing agent in 11 patients (42.3%), second-line in 14 (53.8%), and third-line in 1 (3.85%). The average duration of treatment was 12.1 months. Fourteen patients experienced side effects (53.8%), although most were mild (26.9%). One patient died after a sigmoid colon perforation (3.85%). Overall 22 patients demonstrated clinical improvement during MMF treatment (84.6%). Thirteen patients achieved complete ulcer healing (50%), 10 while taking MMF and 3 after ceasing it.

Limitations: This is a retrospective study based on a single-center cohort.

Conclusion: Our experience suggests that MMF is highly efficacious in PG together with prednisolone, or as part of combination therapy with other immunosuppressants. (J Am Acad Dermatol 2013;69:565-9.)

Key words: autoimmune disease; immunosuppression; mycophenolate mofetil; mycophenolate sodium; pyoderma gangrenosum; steroid-sparing agent; ulcers.

Pyoderma gangrenosum (PG) is a relatively rare inflammatory disease causing cutaneous ulceration. Although corticosteroids and cyclosporine are the mainstays of treatment, mycophenolate mofetil (MMF) (Cellcept; Roche, Nutley, NJ) has emerged as a promising new steroid-sparing agent with comparatively fewer side effects.[1-3] As PG is uncommon, recommendations for MMF have thus far been based on small case series and case reports. This article represents the largest series of patients with PG treated with MMF to date.

METHODS

We identified all patients with PG at our institution treated with MMF from January 2001 to July 2012. All had been treated by an experienced clinician (R. K.). Data were collected from the medical records.

The diagnosis of PG was verified by obtaining documentation of a history of painful ulcers (with or without pathergy or underlying disorders), classic ulcer appearance, a biopsy to exclude other pathology, and response to immunosuppressive treatment.[4] Ulcer size was estimated by measuring height and width as documented in the notes. The

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response to MMF was rated by the treating clinician according to the ease of treatment and presence of complications, independent of the rate of response. Continual improvement without complications was rated "excellent," improvement complicated by flares or side effects was rated "good," and treatment without improvement was rated "ineffective." Treatment for 1 month or less was considered an inadequate trial. Patients were considered to be on monotherapy if there were no other immunosuppressants apart from prednisolone and MMF (excluding antibiotics, local measures, and treatments for comorbidities).

The cumulative duration of inpatient care was calculated from admissions at our institution for which PG or its treatment was a main issue; admissions for comorbid or unrelated conditions were excluded. Ethics approval for this study was obtained from the research governance unit at our institution.

CAPSULE SUMMARY

- Pyoderma gangrenosum is a relatively rare condition for which mycophenolate mofetil represents a promising new treatment, but current experience with this drug is limited.
- In our comparatively large case series mycophenolate mofetil was tolerated well as a steroid-sparing agent and 85% showed a good or excellent response.
- Gastrointestinal side effects were most common and changing to enteric-coated mycophenolate sodium may increase tolerability.

RESULTS

Demographics

In all, 26 patients were identified, 14 female and 12 male. The mean age at commencement of MMF was 66.3 years (range 19-90) with a mean duration of symptoms of 18.5 months (range 1-180). At time of chart review 5 patients were dead with an average age of death of 75.4 years.

Clinical features

One patient presented with bullous PG; the remainder had classic PG. The majority had lower limb ulcer(s) (24 of 26). One patient had an ulcer on the back and another had ulcers at various recent surgical sites. Nine patients had a single ulcer (34.6%), 12 patients had 2 to 4 ulcers (46.2%), and 4 patients had 5 or more ulcers (15.4%). One patient did not have the exact number of ulcers documented, however was likely to have had 5 or more.

Associated systemic conditions

Nine patients had associated systemic diseases (34.6%), including rheumatoid arthritis (4), Crohn's disease (2), chronic lymphocytic leukemia (1), myelodysplasia (1), and chronic small vessel vasculitis (1). Three patients had solid malignancies (prostate cancer, breast cancer, and melanoma). The solid and hematologic malignancies were all diagnosed many years prior and were stable at time of development of PG, with the exception of the melanoma, which was diagnosed simultaneously with the PG then subsequently excised.

Investigations

All patients had routine baseline and follow-up investigations to establish the diagnosis, look for underlying causes, and monitor therapy (full blood cell count, electrolyte panel, liver function tests, blood-borne virus serology, chest x-ray, and skin biopsy). The most common histologic findings were vasculitis, neutrophilic infiltration, and chronic inflammation. Deep fungal culture, mycobacterial culture, and *Mycobacterium ulcerans* polymerase chain reaction were also performed in selected patients. Patients tested for antineutrophil cytoplasmic antibodies, extractable nuclear antigens, and paraproteins all returned negative results. Of the 22 patients tested for antinuclear antibodies, 13 were negative (59%), 5 had a titer of 1:160, and 4 had a titer of 1:40. Most antinuclear antibody–positive patients had an underlying systemic condition (4 rheumatoid arthritis, 2 Crohn's disease, 1 myelodysplasia).

Features of treatment

In our series MMF was used as a first-line steroid-sparing agent in 11 patients (42.3%), second-line in 14 patients (53.8%), and third-line in 1 patient (3.85%). MMF was the main form of mycophenolate used, with mycophenolate sodium (Myfortic; Novartis, Basel, Switzerland) used only when MMF was not tolerated.

The starting dose of MMF was 1 g (24/26) or 2 g (2/26) total daily. Generally the maintenance dose was 2 g (10/26) or 3 g total daily (13/26). Two patients were maintained on 1 g total daily and 1 patient only took MMF for a month at the starting dose before ceasing it. The average duration of treatment was 12.1 months (range 1-56).

Concomitant treatment during MMF therapy

In addition to MMF, all patients received prednisolone and regular wound dressings. The mean prednisolone dose was 40 mg daily at time of starting MMF (mode 50 mg; range 15-80 mg), which was reduced to