Mycophenolate mofetil (MMF) in the treatment of epidermolysis bullosa acquisita (EBA) long-term follow-up

Naveed Sami, MD
Birmingham, Alabama

Key words: epidermolysis bullosa acquisita; mycophenolate mofetil; treatment.

Epidermolysis bullosa acquisita (EBA) is an autoimmune mucocutaneous blistering disease.[1,2] Cutaneous involvement presents with blisters primarily on trauma-prone areas healing with milia.[1,2] Mucosal involvement can lead to irreversible scarring. The treatment of EBA is based on anecdotal reports in the literature with systemic therapies.[3-7] Mycophenolate mofetil (MMF) is an immune-suppressing agent that has been reported to be effective in the treatment of autoimmune mucocutaneous blistering diseases.[3,4,8-11] This report describes the successful treatment of 4 patients with EBA using MMF as a steroid-sparing agent at our center along with a long term follow-up.

CASE SERIES

This retrospective study consisted of 4 patients with EBA treated with MMF, and was conducted with the approval of the institutional review board of the University of Alabama at Birmingham. The diagnosis was confirmed in all 4 patients with a skin biopsy specimen, immunopathology, and serology.[1,2] Skin biopsy specimens demonstrated a subepidermal split with a mixed inflammatory infiltrate on routine histology, and IgG binding along the basement membrane zone on direct immunofluorescence. Serological studies with indirect immunofluorescence demonstrated antibasement membrane zone antibodies using monkey esophagus as substrate and autoantibody binding to the dermal side of the salt-split skin. The response to MMF treatment was assessed based on the following criteria: (1) healing of involvement of the initial presentation; and (2) absence of new lesions. Complete control was defined as patients meeting both response criteria 1 and 2 and discontinuing systemic corticosteroids. Partial control was defined as patients meeting only criteria 1 and being unable to discontinue steroids.

Two patients were male and 2 were female. The age at onset ranged from 48 to 86 (mean 61) years. All patients had both mucosal and cutaneous involvement. The most common areas of mucosal involvement included oral (4), nasal (4), pharyngeal (2), and laryngeal (1). The patient with laryngeal involvement required a tracheostomy. Cutaneous involvement was present on the extremities and acral surfaces and amount of body surface area involvement is presented in Table I.

All patients were initially treated with prednisone with dosages ranging between 40 and 60 mg/d. Steroid-sparing agents before MMF included the following with their dosages: azathioprine (100-200 mg/d), dapsone (100-200 mg/d), colchicine (0.6-1.2 mg/d), and tetracycline (2 g/d). The duration of systemic treatments before starting MMF ranged between 16 and 26 (mean 22) months. All 4 patients received MMF with a dosage ranging between 2 and 3 g/d. An effective response to MMF was observed after 4 to 12 (mean 7) months and the dosage of prednisone was gradually reduced. Three patients achieved complete control and 1 patient had partial control because he was unable to taper below 10 mg/d of prednisone. However, this was the lowest dosage he was able to achieve after failing to respond to previous treatments. The details of each patient are presented in Table I. Local supportive care was also recommended including avoiding trauma and infection, and the use of the following

From the Department of Dermatology, University of Alabama at Birmingham.
Funding sources: None.
Conflicts of interest: None declared.
Correspondence to: Naveed Sami, MD, Department of Dermatology, University of Alabama at Birmingham, 1520 Third Ave S, EFH 414, Birmingham, AL 35294-0009. E-mail: nsami@uabmc.edu.

JAAD Case Reports 2015;1:321-3.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2015.07.007

Table I. Clinical features, prior treatments, and mycophenolate mofetil treatment of epidermolysis bullosa acquisita

Age at onset, y/gender	Clinical features (mucosal/cutaneous BSA)	Prior treatments to MMF	Duration of prior treatments, mo	MMF (maximum) dosage for control, g/d	Response
48/F	Oral, nasal, pharyngeal, laryngeal 20% BSA	Prednisone (40 mg/d)	N/A	2	Complete control
53/F	Oral, nasal, pharyngeal 20% BSA	Prednisone (40 mg/d) Dapsone (100 mg/d) Azathioprine (100 mg/d)	16	3	Complete control
56/M	Oral, nasal 20% BSA	Prednisone (60 mg/d) Tetracycline (2 g/d) Dapsone (200 mg/d) Colchicine (1.2 mg/d) Azathioprine (200 mg/d)	24	3	Partial control
86/M	Oral, nasal 30% BSA	Prednisone (60 mg/d) Dapsone (100 mg/d) Colchicine (1.2 mg/d)	26	2	Complete control

BSA, Body surface area involved (cutaneous); *F*, female; *M*, male; *MMF*, mycophenolate mofetil; *N/A*, MMF was started with prednisone.

topical corticosteroid creams to affected areas to facilitate healing: triamcinolone 0.1%, betamethasone diproprionate 0.05%, and halobetasol propionate 0.05%. After a mean follow-up period of 9 years (range 4-12 years) only 1 of the 4 patients was able to discontinue MMF.

DISCUSSION

MMF is an immune-suppressing agent that has been used in the treatment of autoimmune mucocutaneous blistering disease.[3,4] However, there are very few case reports that have described its use in EBA.[8-11]

This study described 4 patients who were successfully treated with MMF for extensive involvement with EBA. MMF was instituted as a steroid-sparing agent after failure of response was observed to multiple conventional treatments. Three of the 4 patients were able to completely discontinue systemic corticosteroids and establish complete control of their disease with just MMF as monotherapy. This included 1 patient with laryngeal involvement requiring a tracheostomy who is currently only taking MMF at 500 mg/d as monotherapy while maintaining complete control. She has also underwent successful removal of her T-tube and repair of the open anterior tracheal wall with no further issues with breathing or swallowing and her voice has remained stable.

Although the precise mechanism of action of MMF in EBA is unclear, MMF is an immune suppressant that has been shown to inhibit the proliferation of B and T lymphocytes.[4] This could lead to a decrease in the production of autoantibodies, specifically to collagen VII, resulting in clinical control of the disease.

MMF has been reported to have multiple side effects including gastrointestinal, genitourinary, infectious, and neurologic.[3] Two of our patients reported gastrointestinal side effects when they were taking dosages greater than 2.5 g/d and resolved in both patients when the dosage was reduced to 2 g/d.

Because EBA is a chronic disease, the length of therapy can vary widely. We have been unsuccessful in discontinuing MMF as monotherapy in 2 of the 3 patients in the complete control group. An attempt to slowly taper the MMF in 1 patient when she had been stable at 2 g/d for 2 years resulted in an exacerbation with nasal involvement and localized scarring after reaching a dosage of 500 mg/d. Complete control of the disease was re-established in this patient by increasing the dosage of MMF to 2 g/d. Hence, MMF may be necessary as long-term maintenance treatment in some patients.

There are several limitations to this study including a very small cohort of patients and lack of a control group. The use of MMF is also limited by the higher cost of the medication compared with other oral conventional alternative agents. Because treatment choices are limited, MMF could still be a viable alternative for patients with EBA who have contraindications to or failed other systemic therapies. Larger multicenter randomized controlled trials are needed to evaluate the efficacy and role of MMF for the treatment of EBA.

REFERENCES

1. Gupta R, Woodley DT, Chen M. Epidermolysis bullosa acquisita. *Clin Dermatol*. 2012;30:60-69.
2. Caux F. Diagnosis and clinical features of epidermolysis bullosa acquisita. *Dermatol Clin*. 2011;29:485-491.

3. Meurer M. Immunosuppressive therapy for autoimmune bullous diseases. *Clin Dermatol*. 2012;30:78-83.
4. Culton DA, Diaz LA. Treatment of subepidermal immunobullous diseases. *Clin Dermatol*. 2012;30:95-102.
5. Intong LR, Murrell DF. Management of epidermolysis bullosa acquisita. *Dermatol Clin*. 2011;29:643-647.
6. Kubisch I, Diessenbacher P, Schmidt E, Gollnick H, Leverkus M. Premonitory epidermolysis bullosa acquisita mimicking eyelid dermatitis: successful treatment with rituximab and protein A immunoapheresis. *Am J Clin Dermatol*. 2010;11:289-293.
7. Czernik A, Toosi S, Bystryn JC, Grando SA. Intravenous immunoglobulin in the treatment of autoimmune bullous dermatoses: an update. *Autoimmunity*. 2012;45:111-118.
8. Schattenkirchner S, Eming S, Hunzelmann N, Krieg T, Smola H. Treatment of epidermolysis bullosa acquisita with mycophenolate mofetil and autologous keratinocyte grafting. *Br J Dermatol*. 1999;141:932-933.
9. Marzano AV, Dassoni F, Caputo R. Treatment of refractory blistering autoimmune diseases with mycophenolic acid. *J Dermatolog Treat*. 2006;17:370-376.
10. Kowalzick L, Suckow S, Ziegler H, et al. Mycophenolate mofetil in epidermolysis bullosa acquisita. *Dermatology*. 2003;207:332-334.
11. Tran MM, Anhalt GJ, Barrett T, Cohen BA. Childhood IgA-mediated epidermolysis bullosa acquisita responding to mycophenolate mofetil as a corticosteroid-sparing agent. *J Am Acad Dermatol*. 2006;54:734-736.