

Adjuvant Therapy of Bullous Pemphigoid with Mycophenolate Mofetil: Old Drug, New Use

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ABSTRACT

Bullous Pemphigoid (BP) is an autoimmune subepidermal blistering disease appearing predominantly in the elderly. The disease is primarily treated with systemic corticosteroids. However, the treatment can be associated with significant morbidity. Adjuvant corticosteroid sparing therapy can also be associated with significant morbidity. In this study a case of BP which was difficult to control with systemic steroids was successfully treated with mycophenolate mofetil as adjuvant therapy. Mycophenolate mofetil used previously in transplantation, has recently been shown to be useful in autoimmune blistering disorders. Further study to confirm this significant finding and to determine if the long term prognosis of BP can be altered by the drug, is required.

Keywords: Bullous Pemphigoid, mycophenolate mofetil

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INTRODUCTION

Bullous Pemphigoid (BP)⁽¹⁾ is a subepidermal autoimmune disease presenting as pruritus, papulovesicles and tense blisters. It is characterised by linear deposition of IgG and C3 at the cutaneous basement membrane zone⁽²⁾. Autoantibodies in BP are directed against two hemidesmosomal proteins designated BP230 and BP180⁽³⁾.

Mycophenolate mofetil was approved by the US Food and Drug Administration in 1995 primarily for renal and other organ allografts to prevent rejection⁽⁴⁾. It is also very recently been used to treat bullous pemphigoid⁽⁵⁾.

In this report, an elderly women with BP repeatedly relapsed while on prednisolone therapy. The addition of adjuvants like methotrexate and azathioprine could not be tolerated. She was successfully treated with mycophenolate mofetil as a steroid sparing agent.

CASE REPORT

A sixty-two-year-old female first presented in 1993 with tense blisters on the limbs and abdomen. Conjunctiva,

scalp and mouth were normal. Biopsy of one of the blisters on H and E section showed a subepidermal cleavage with a mixed dermal infiltrate of polymorphs, lymphocytes and eosinophils. The picture was consistent with BP. Direct immunofluorescence of perilesional skin showed smooth linear deposits of C3 and IgG along the dermoepidermal junction. Sodium chloride split skin showed deposits of IgG on the roof. Systems review revealed no obvious malignancy. Full blood counts, blood sugar, renal function and liver function tests were all normal. A diagnosis of BP was made and she was started on 60 mg of prednisolone daily. However, fresh blisters kept appearing after two weeks. Dapsone 100 mg daily was added as an adjuvant. Although her blood counts remained normal, two weeks later she developed pruritic maculopapular dermatitis. Hypersensitivity to Dapsone was suspected and the drug was discontinued. She remained on 60 mg prednisolone for a further six weeks after which the disease appeared to be under control. The steroids were gradually tapered to 15 mg over the next year. However, when the steroids were reduced to 10 mg/day a moderate flare of BP occurred. Prednisolone had to be increased again to 45 mg/day. During this period she also developed extensive tinea corporis on her trunk and limbs. The fasting blood sugar had risen to 15.8 mmol/L. Tolbutamide was commenced to control her steroid induced diabetes. Her tinea corporis was only partially responsive to Miconazole cream and oral Itraconazole and Terbinafine.

Over the next two years, many attempts to reduce the Prednisolone to 10 mg/day resulted in relapses. BP control was satisfactory only when the Prednisolone was increased to between 45 mg to 60 mg daily. Methotrexate was then added as adjuvant therapy. However, after one month treatment with 10 mg/week of methotrexate, her haemoglobin decreased to 7 gm from 12 gm. She concurrently developed mild cardiac failure. Methotrexate was discontinued and she was transfused with packed cells. Her diabetes remained difficult to control and she was differing from recurring and extensive tinea corporis. She was then commenced on 150 mg/day of Azathioprine as an adjuvant to

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Prednisolone. However, after two weeks, she developed severe abdominal pain and vomiting which ceased when Azathioprine was discontinued. In 1999, Mycophenolate mofetil (Cellcept®) 500 mg twice a day was commenced in addition to 15 mg/day Prednisolone. After two months of Cellcept®, it was possible for the first time to gradually decrease the Prednisolone dose to 2.5 mg/day. Her diabetic medication was reduced as her blood sugar was now stable. Her extensive tinea corporis cleared without any treatment. At the time of writing, she was maintained on 2.5 mg/day Prednisolone and 1 gm/day Cellcept® and has been free of relapse for some six months.

DISCUSSION

BP is the most frequent of the autoimmune subepidermal blistering disease occurring mainly in older patients. It is characterised by tense blisters on an erythematous base especially in the intertriginous areas and is usually not accompanied by mucous membrane lesions⁽⁶⁾. BP increases rapidly beyond the age of 60 years⁽⁷⁾. It is expected that as the population ages in Singapore, the incidence of BP will increase. Many variants of the disease like cicatricial pemphigoid have been reported⁽⁸⁾. Ultrastructurally, the blister is formed by separation occurring through the lamina lucida. These patients possess IgG autoantibodies reactive against the major antigens BPAG1 and BPAG2, produced by autoreactive T-cell clones which are thought to be responsible for blister formation⁽⁸⁾.

The treatment of BP as with many other autoimmune disorders can include oral and topical corticosteroids; anti proliferative drugs like Methotrexate, Cyclophosphamide and Azathioprine. Inhibitors of T-cell activation like Cyclosporine and polymorphonuclear leukocyte inhibitors like Dapsone have also been used in the control of BP. However, all these drugs have been associated with significant morbidity especially in the elderly. In localised BP, topical steroids have been reported to be useful⁽⁹⁾. However, the vast majority of BP patients are of moderate to severe in extent and require systemic steroids⁽¹⁰⁾. Multicentre studies of oral steroids in patients with BP have demonstrated the need in many patients of a second drug to achieve or maintain remission⁽¹⁰⁾. Dapsone as monotherapy is only useful in patients with cicatricial pemphigoid⁽¹¹⁾ and is generally effective only in a minority of patients with BP⁽¹⁰⁾. Most patients with BP therefore require either Azathioprine or Cyclophosphamide or Methotrexate for steroid sparing (adjuvant) effect to achieve complete remission⁽¹⁰⁾. To date no evidence based studies exist to distinguish between the relative merits of the above mentioned adjuvant drugs. It is therefore a matter of personal experience balancing

the possible contraindications versus the toxic effects that dictate choice. In an elderly with pre-existing liver disease, Methotrexate and Azathioprine would be contraindicated. Likewise any pre-existing bladder pathology would preclude the use of Cyclophosphamide. Some patients have been treated with Cyclosporine and systemic steroids⁽¹²⁾. However, Cyclosporine alone is rarely beneficial⁽¹⁰⁾ and is contraindicated in patients with renal dysfunction (especially in the elderly).

This case presented with BP and was treated with systemic steroids. However, there were complications due to the steroid therapy. Attempts to introduce conventional adjuvant therapy like Methotrexate and Azathioprine resulted in side effects which necessitated cessation of these adjuvant drugs. The introduction of Mycophenolate mofetil resulted in satisfactory steroid sparing and allowed the disease to be well controlled. Mycophenolate mofetil is an ester product of the active immunosuppressant mycophenolic acid⁽¹³⁾. Originally isolated as a fermentation product of *Penicillium stoloniferum*, it selectively inhibits inosine monophosphate dehydrogenase. This enzyme is critical in the de novo synthesis of guanosine nucleotides for DNA synthesis. B and T lymphocytes unlike other cell types are dependent on the de novo pathway for guanosine synthesis because these lymphocytes are unable to use the salvage guanosine synthesis pathway⁽¹⁴⁾. Mycophenolate mofetil has recently been used to treat BP⁽¹⁵⁾ and another autoimmune bullous disease pemphigus vulgaris⁽¹⁶⁾ and Psoriasis⁽¹⁷⁾ in white patients. To the best of the author's knowledge there has been very little documented experience in Asian BP patients on the use of Mycophenolate mofetil. The side effects of Mycophenolate mofetil include nausea, vomiting, diarrhoea, increased incidence of herpes zoster infections and bone marrow suppression. Unlike other cytotoxic steroid sparing adjuvant therapies for BP, it does not have significant risk of renal or hepatic toxicity⁽¹⁸⁾. Originally, Mycophenolate mofetil was successfully used to prolong graft survival but has recently been used to treat various inflammatory diseases⁽¹⁷⁾. This case presented with BP and was treated with systemic steroids. However, there were serious complications due to the steroid therapy. Attempts to introduce conventional adjuvant therapy resulted in side effects which necessitated cessation of the adjuvant drugs. Although Mycophenolate mofetil is significantly more expensive than other cytotoxic agents, it was the only drug the patient was able to tolerate and it resulted in satisfactory steroid sparing and permitted the disease to be well controlled. The elderly are prone to have pre-existing illnesses, therefore it is very important to appreciate the different types of steroid sparing agents available with toxic

side effects that affect different organs. This will allow for the most appropriate choice of adjuvant therapy in each patient. In this study, Mycophenolate mofetil was an effective sparing agent. It is still unclear if the drug has a significant effect on the long term outcome on the disease. More studies need to be conducted to observe the effect of the drug on the induction of remission in patients with autoimmune blistering diseases.

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