# Bullous Pemphigoid Treated With Intravenous Immunoglobulin

Papapit Tuchinda, MD; Simon Ritchie, MD; Anthony A. Gaspari, MD

**Practice Points**

- Intravenous immunoglobulin monotherapy may be a treatment option for bullous pemphigoid patients.
- Due to the high cost of intravenous immunoglobulin, treatment should be reserved for special cases.

*Bullous pemphigoid (BP) is a blistering autoimmune disease that primarily affects elderly patients who commonly present with comorbidities. Side effects from long-term treatment with conventional cytotoxic and immunosuppressive agents may increase morbidity and mortality in this patient population. We present a case of BP in a 78-year-old woman with an active pulmonary* Mycobacterium avium-intracellulare complex *(MAC) infection that precluded the use of systemic corticosteroids or other immunosuppressants. Our patient was successfully treated with intravenous immunoglobulin (IVIG) monotherapy, which may provide an alternative treatment option for BP patients who are unable to tolerate cytotoxic or immunosuppressive therapies.*

*Cutis.* 2014;93:264-268.

Bullous pemphigoid (BP) is an autoimmune vesiculobullous disease. Systemic corticosteroids are the mainstay of treatment, but they may cause serious side effects. Other alternative treatments may be combined as steroid-sparing agents but most still lead to immunosuppression or cytotoxicity.

We present a case of BP in a 78-year-old woman with an active pulmonary *Mycobacterium avium-intracellulare complex* (MAC) infection that precluded the use of systemic corticosteroids or other immunosuppressants. Our patient was successfully treated with intravenous immunoglobulin (IVIG) monotherapy, which may provide an alternative treatment option for BP patients who are unable to tolerate cytotoxic or immunosuppressive therapies.

## Case Report

A 78-year-old woman with a history of BP and pulmonary infection with MAC was referred to our clinic for management options. Her BP initially was controlled with potent topical corticosteroids, tetracycline, dapsone, and hydroxychloroquine, but they failed to induce a response. A dermatologic examination was notable for numerous tense bullae and ruptured bullae on erythematous bases on the trunk, back, and extremities (Figure, A). A skin biopsy as well as direct and indirect immunofluorescence confirmed the diagnosis of BP. The concurrent pulmonary MAC infection precluded the use of corticosteroids or methotrexate. Intravenous immunoglobulin therapy (1 g/kg daily) for 2 consecutive days each month was initiated. One week after IVIG was initiated, the lesions began to heal and no new lesions had appeared. Over the next 3 infusions, the lesions demonstrated notable improvement, but the patient developed rare new lesions. The indirect immunofluorescence titer decreased from 1:640 at baseline to 1:20 after 4 infusions, which correlated with clinical improvement (Figure, B). The patient received 6 cycles of IVIG and was lost to follow-up.

## Comment

Therapeutic options for treatment of BP consist mainly of corticosteroids, immunosuppressants, systemic antibiotics, immunomodulators, and plasmapheresis. The patient's age, comorbidities, and current medications make treatment more complex. Despite aggressive therapy with protracted courses of high-dose systemic corticosteroids in refractory cases, up to 24% of BP patients do not respond to this treatment method.[1] Some patients

From the Department of Dermatology, University of Maryland, Baltimore. Dr. Tuchinda also is from the Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

The authors report no conflict of interest.

Correspondence: Papapit Tuchinda, MD, Department of Dermatology, University of Maryland School of Medicine, 419 W Redwood St, Ste 240, Baltimore, MD 21201 (papapitt@gmail.com).



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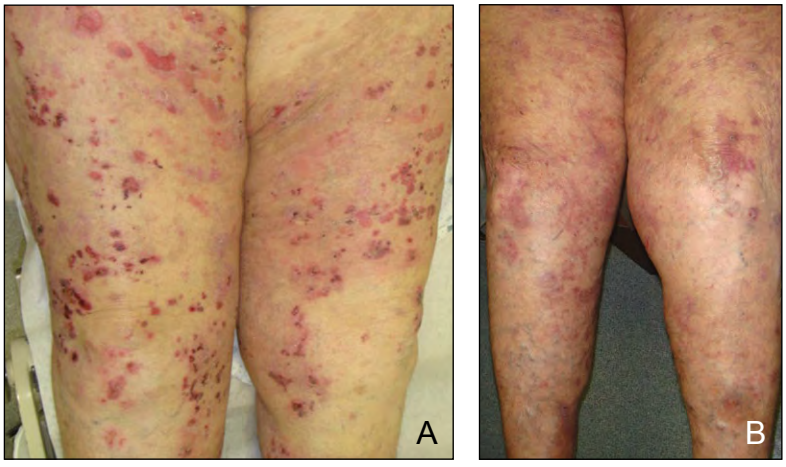


Numerous tense and ruptured bullae on erythematous bases were visible on the legs at initial presentation (A). Four months after initiating intravenous immunoglobulin therapy for bullous pemphigoid, the skin lesions had improved (B).

develop negative side effects from systemic corticosteroid therapy or demonstrate no results with low doses of corticosteroids as maintenance therapy.

Negative side effects associated with BP treatment (eg, infection, immunosuppression, adverse drug reaction) are of serious concern in elderly patients who are disproportionately affected with BP. An association between mortality and therapeutic complications has been reported, especially in patients who have been treated with high doses of oral prednisolone or have undergone long-term treatment with immunosuppressive agents.[2-4] The principal causes of death are prolonged immunosuppression leading to sepsis and cardiovascular disease.[5,6] The predictors of mortality in the first year after diagnosis are older age, higher doses of systemic corticosteroids, and low levels of serum albumin.[7]

In our patient, systemic corticosteroids and other immunosuppressive agents were contraindicated because of an active pulmonary infection. Because of its potential efficacy and lack of immunosuppressive side effects, we decided to treat our patient with IVIG therapy.

Intravenous immunoglobulin, an immunomodulatory agent, has been reported as an alternative therapy in patients with BP (Table).[1,8-12] According to the consensus statement on the use of IVIG therapy in the treatment of autoimmune mucocutaneous blistering diseases, indications for IVIG treatment include failed conventional therapy; serious adverse effects from conventional therapy; contraindications regarding the use of high-dose, long-term systemic corticosteroids or immunosuppressants; progressive disease despite maximum conventional systemic therapy; or uncontrolled, rapidly debilitating progressive disease.[13]

Many mechanisms of action for IVIG have been proposed, including blockage of the Fc receptor, diminution of circulating antibody titers by a neonatal Fc receptor–mediated mechanism, cytokine-mediated effects, complement-mediated effects, effects on apoptosis, toxin neutralization, and/or modification of steroid sensitivity.[13-16]

High-dose IVIG therapy usually consists of a 2-g/kg cycle, with each cycle divided into 2 or 3 consecutive infusions.[3,13] The interval between cycles is every 4 weeks until the patient has achieved a clinical response with no new lesions for at least 3 weeks and healing of the remaining lesions.[13] After clinical control is achieved, the dosing interval gradually is increased to 16 weeks; if no new lesions develop within 16 weeks, therapy may be tapered and discontinued.[1,3]

Anti-BP180 and anti-BP230 titers tend to diminish after 3 months of IVIG therapy and usually are undetectable after 10 to 11 months.[3,17] Combination therapy of IVIG and immunosuppressive agents may cause greater reductions in serum levels of BP autoantibodies and lower the risk for rebound during withdrawal of IVIG therapy.

The safety profile of IVIG therapy is excellent. In one study, less than 5% of patients who underwent IVIG therapy experienced side effects.[16] Elderly patients with underlying conditions such as hypertension, myocardial infarction, stroke, thrombosis, and hypercoagulability should be closely monitored due to a greater risk for complications.[18]

## Conclusion

We present the case of an elderly patient with BP and an active pulmonary infection who was successfully treated with high-dose IVIG without any side effects. A clinical response was seen within 1 week after initiation of IVIG, and marked improvement of the BP lesions was noted by the end of the fourth infusion. Intravenous immunoglobulin appears to be a valuable option for patients with BP for whom cytotoxic or immunosuppressive therapies are contraindicated or for patients who have failed to respond to conventional therapies. However, IVIG is costly and therefore should be reserved for special cases.[19] Further controlled studies



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## IVIG Therapy in Patients With BP

| Reference (Year) | No. of Patients (Gender) | Age | Prior Systemic Treatment(s) | Mean Duration of Treatment Before IVIG Therapy | IVIG Therapy | Adjunctive Treatment | Time to Clinical Response | IIF Titer Before and After IVIG Therapy | Outcome and Follow-up |
|---|---|---|---|---|---|---|---|---|---|
| Ahmed[1] (2001) | 15 (10 M, 5 F) | 61–89 y | Prednisolone, dapsone, azathioprine, tetracycline, nicotinamide, erythromycin, methotrexate, cyclophospha-mide, cyclosporine | 28.3 mo | 2 g/kg per cycle over 3 d every 4 wk; 10–18 cycles (mean, 14.7 cycles) | N/A | 2–4 mo (mean, 2.9 mo) | Before IVIG, 1:80 or greater; after IVIG, N/A | Discontinuation of adjuvant drugs with no relapse; none of the patients needed prednisolone during follow-up |
| Engineer and Ahmed[8] (2001) | 17 (9 M, 8 F) | 64–82 y | Prednisolone, azathioprine, methylprednisolone, dexamethasone | 3 mo to >30 y | 100 mg/kg/d for 5 d (n=1); 300 mg/kg/d for 5 d (n=1); 400 mg/kg/d for 5 d (n=15) (total no. of cycles: 1 [n=12], 2 [n=4], 3 [n=1]) | 7 patients received adjuvant therapy includ-ing prednisolone, dexamethasone, plasmapheresis, azathioprine, dapsone | N/A | N/A | Discontinuation or reduction of adjuvant drugs (n=12); condition unchanged (n=5); no im-provement was observed in patients who received low-dose IVIG or a single treat-ment cycle |
| Xiao et al[9] (2007) | 1 (1M) | 3.5 mo | None | None | 400 mg/kg/d (5 g/d) for 4 d | N/A | 1 wk | Before IVIG, BP180 serum level was 57 U/mL; after IVIG, N/A | No relapse at 2 y follow-up |



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|---|---|---|---|---|---|---|---|---|---|
| Sugawara et al[10] (2007) | 1 (1M) | 3 mo | Prednisolone, erythromycin, dapsone, dexamethasone, methylprednisolone pulse therapy | 2 mo | 300 mg/kg/d (2.5 g/d) for 5 d (2 courses) | Dexametha-sone, erythro-mycin, dapsone | 1 wk | Before IVIG, 1:80; after IVIG, N/A | Discontinuation of adjuvant drugs after second course of IVIG; no relapse at 16 mo follow-up |
| Czernik and Bystryn[11] (2008) | 1 (N/A) | 78 y | Prednisolone, mycophenolate mofetil | 5 mo | 19 cycles of IVIG every 2–4 wk over 16 mo | Prednisolone, mycophenolate mofetil, azathioprine | 2 mo | Before IVIG, 1:320; after IVIG, 1:20 (autoantibody level decreased during adjunc-tive therapy but increased during IVIG monotherapy) | Discontinuation of immunosuppres-sive drug; reduction of prednisolone to 10 mg/d; new lesions developed at a rate of 1 bulla per wk |
| Cruz et al[12] (2013) | 1 (1M) | 38 y | Prednisolone, azathioprine, mycophenolate mofetil, rituximab | 1 mo | 2 g/kg per cycle every 4 wk | Prednisolone, mycophenolate mofetil, rituximab, dapsone | N/A | Before IVIG, BP180 serum level was 228 U/mL and BP230 serum level was 36 U/mL; after IVIG, N/A | Patient died 2.5 y after onset of disease |

Abbreviations: IVIG, intravenous immunoglobulin; BP, bullous pemphigoid; IIF, indirect immunofluorescence; M, male; F, female; N/A, not available.



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are necessary to confirm the role and benefit of IVIG for the treatment of BP in patients such as ours.

## REFERENCES


1. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol.* 2001;45:825-835.
2. Venning VA, Wojnarowska F. Lack of predictive factors for the clinical course of bullous pemphigoid. *J Am Acad Dermatol.* 1992;26:585-589.
3. Ishii N, Hashimoto T, Zillikens D, et al. High-dose intravenous immunoglobulin (IVIG) therapy in autoimmune skin blistering diseases. *Clin Rev Allergy Immunol.* 2010;38:186-195.
4. Joly P, Roujeau JC, Benichou J, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med.* 2002;346:321-327.
5. Roujeau JC, Lok C, Bastuji-Garin S, et al. High risk of death in elderly patients with extensive bullous pemphigoid. *Arch Dermatol.* 1998;134:465-469.
6. Khumalo NP, Murrell DF, Wojnarowska F, et al. A systematic review of treatments for bullous pemphigoid. *Arch Dermatol.* 2002;138:385-389.
7. Rzany B, Partscht K, Jung M, et al. Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol.* 2002;138:903-908.
8. Engineer L, Ahmed AR. Role of intravenous immunoglobulin in the treatment of bullous pemphigoid: analysis of current data. *J Am Acad Dermatol.* 2001;44:83-88.
9. Xiao T, Li B, Wang YK, et al. Childhood bullous pemphigoid treated by iv immunoglobulin. *J Dermatol.* 2007;34:650-653.
10. Sugawara N, Nagai Y, Matsushima Y, et al. Infantile bullous pemphigoid treated with intravenous immunoglobulin therapy. *J Am Acad Dermatol.* 2007;57:1084-1089.
11. Czernik A, Bystryn JC. Improvement of intravenous immunoglobulin therapy for bullous pemphigoid by adding immunosuppressive agents: marked improvement in depletion of circulating autoantibodies. *Arch Dermatol.* 2008;144:658-661.
12. Cruz MJ, Santos P, Morais P, et al. Refractory bullous pemphigoid with fatal outcome in a young patient. *Int J Dermatol.* 2013;52:601-602.
13. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol.* 2003;139:1051-1059.
14. Jolles S, Hughes J, Whittaker S. Dermatological uses of high-dose intravenous immunoglobulin. *Arch Dermatol.* 1998;134:80-86.
15. Jolles S. High-dose intravenous immunoglobulin (hdIVIg) in the treatment of autoimmune blistering disorders. *Clin Exp Immunol.* 2002;129:385-389.
16. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med.* 2001;345:747-755.
17. Sami N, Ali S, Bhol KC, et al. Influence of intravenous immunoglobulin therapy on autoantibody titres to BP Ag1 and BP Ag2 in patients with bullous pemphigoid. *J Eur Acad Dermatol Venereol.* 2003;17:641-645.
18. Ruetter A, Luger TA. Efficacy and safety of intravenous immunoglobulin for immune-mediated skin disease: current view. *Am J Clin Dermatol.* 2004;5:153-160.
19. Mutasim DF. Autoimmune bullous dermatoses in the elderly: an update on pathophysiology, diagnosis and management. *Drugs Aging.* 2010;27:1-19.






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