Omalizumab therapy for bullous pemphigoid

Kenneth K. Yu, PhD,[a] Ashley B. Crew, MD,[a] Kelly A. N. Messingham, PhD,[b]
Janet A. Fairley, MD,[b,c] and David T. Woodley, MD[a,d]
Los Angeles, California, and Iowa City, Iowa

Background: Bullous pemphigoid (BP) responds to a variety of immunosuppressive agents and usually controls, but does not cure, the disease. Omalizumab, Food and Drug Administration–approved for asthma, selectively suppresses the activity of IgE, an important immunoglobulin in the pathogenesis of BP.

Objective: We wished to determine if systemic omalizumab would have a therapeutic effect in patients with BP.

Methods: We treated 6 patients with BP using omalizumab and followed up their disease for up to 42 months.

Results: Although variable, 5 of the 6 patients with BP received therapeutic benefit from systemic omalizumab (the sixth terminated treatment because of intercurrent illness) with less use of other immunosuppressants, inhibition of new bullae, less pruritus, and dramatic decreases in eosinophil counts. None of the patients had untoward side effects from omalizumab.

Limitations: This was an open, uncontrolled study.

Conclusions: Omalizumab neutralizes the activity of IgE in patients with BP and improves the control of their disease activity. (J Am Acad Dermatol 2014;71:468-74.)

Key words: autoimmunity; bullous pemphigoid; IgE; omalizumab; pruritus.

Bullous pemphigoid (BP) is an acquired autoimmune bullous disease characterized by autoantibodies against 2 skin basement membrane zone (BMZ) proteins: type XVII collagen, a 180-kd protein (bullous pemphigoid antigen 2), and the 230-kd BP antigen (bullous pemphigoid antigen 1) found within the hemidesmosomes of basal keratinocytes.[1,2] Patients with BP develop tense skin blisters on inflammatory skin, and often experience pruritus and urticaria-like erythematous skin lesions. IgG is the predominant antibody against the BMZ components, but studies have shown that a majority (70%) of patients with BP also have elevated levels of serum IgE,[3-7] and 25% of patients with BP also have IgE deposits at the BMZ.[8] Standard therapies for BP consist of corticosteroids and immunosuppressants, which are associated with significant morbidity.[9] Therefore, a general treatment goal for BP is to use the lowest possible dose of systemic steroids. Nevertheless, nonsteroidal immunosuppressive agents also carry

Abbreviations used:

BMZ:	basement membrane zone
BP:	bullous pemphigoid
BP180:	bullous pemphigoid 180 kDa antigen
BP230:	bullous pemphigoid 230 kDa antigen
ELISA:	enzyme-linked immunosorbent assay
IF:	immunofluorescence

From the Keck School of Medicine, University of Southern California[a]; Carver College of Medicine, University of Iowa[b]; and Department of Veterans Affairs Medical Centers in Iowa City[c] and Los Angeles.[d]

This material is based on work supported in part by VA Merit Review grant 1I01CX000317-01 (Dr Fairley) from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development 1BX001680-01.

Conflicts of interest: None declared.

Accepted for publication April 21, 2014.

Reprint requests: David T. Woodley, MD, Keck School of Medicine, University of Southern California, USC/Norris Cancer Center, Topping Tower #3405, 1441 Eastlake Ave, Los Angeles, CA 90033. E-mail: dwoodley@usc.edu.

Published online June 23, 2014.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.04.053

significant potential side effects, especially with prolonged use.

Omalizumab, a treatment for asthma,[10] is a humanized monoclonal antibody that blocks the binding of IgE to its receptors. Compared with systemic corticosteroids, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil, the mechanism of action of omalizumab is more selective. Therefore, omalizumab may have a more benign side-effect profile than the conventional agents for BP. Herein, we report 6 cases that illustrate the use of omalizumab in the management of BP. Preliminary results on patients 1 and 4 were previously reported[11,12] and updated information on their long-term treatment is contained in this report.

CAPSULE SUMMARY

- A role for IgE class autoantibodies in bullous pemphigoid has been demonstrated.
- Herein, 6 patients with pemphigoid were treated with omalizumab, an anti-IgE monoclonal antibody.
- Five of 6 patients had a good response to omalizumab, suggesting that targeting of IgE may be a strategy for the treatment of bullous pemphigoid.

CASE REPORTS

A summary of the salient features of the cases are provided in Table I. Detailed reports of the cases follow.

Patient 1

This female patient's initial treatment was previously reported as part of a trial of omalizumab as monotherapy for BP (IND 100569).[11] During the trial, her body surface involvement with urticarial plaques declined from 50% to 5%, and only a small number of 4- to 6-mm erosions remained (Fig 1). The patient remained clear for 15 weeks, at which point she noticed increased pruritus and a recurrence of skin lesions. Omalizumab was reinstituted at the same dose, the pruritus subsided, and the blisters resolved within 2 weeks. After a 6-dose cycle her skin was clear and omalizumab was discontinued. The patient remained clear for 5 months until she flared with a recurrence of pruritus and blistering. Omalizumab was again reinstituted at the same dose; however, after an initial decrease in her eosinophil count and some improvement in symptoms, her disease recurred while on omalizumab, the medication was discontinued, and she was treated with prednisone and azathioprine.

Patient 2

A 78-year-old woman was referred to University of Southern California for BP. She had pruritus for 18 months when the diagnosis of BP was made by histology, IgG at the BMZ of biopsied skin by direct immunofluorescence (IF), and elevated enzyme-linked immunosorbent assay (ELISA) to bullous pemphigoid 180 kDa antigen (BP180) (90 U, normal <9 U) and bullous pemphigoid 230 kDa antigen (BP230) (115 U, normal <9 U). On 20 mg of prednisone per day, her BP improved, but was still present. Therapy was augmented with niacinamide (2 g daily) and doxycycline (200 mg daily), but her pruritus continued. The addition of multiple antihistamines did not control her symptoms. Despite the addition of 50 mg daily of azathioprine she continued to have persistent pruritus when her prednisone was decreased below 15 mg daily. Because of her disabling pruritus, elevated IgE (615 IU/mL), and osteoporosis associated with continued prednisone use, the decision was made to initiate therapy with omalizumab, 300 mg calculated by weight and IgE level, every 6 weeks. Three months after initiation of omalizumab therapy, she was able to discontinue the use of prednisone and azathioprine. However, she was not able to obtain her next scheduled dose of omalizumab because of difficulty with approval from her insurance company, and subsequently had a relapse of her BP symptoms. Omalizumab was then reinstituted at 300 mg every 8 weeks. New blister formation ceased, but she continued to experience pruritus. Treatment cycles were shortened to every 6 weeks, and her pruritus improved, but did not resolve completely. Treatment cycles were further shortened to every 4 weeks, and she now experiences only intermittent pruritus that is controlled readily with antihistamines fexofenadine (180 mg daily) and hydroxyzine (50 mg at bedtime as needed). We have continued her on this omalizumab regimen, and she has remained free of skin lesions for the last 20 months.

Patient 3

A 72-year-old woman presented with a 7-month history of highly pruritic plaques that evolved into tense blisters on erythematous bases. Histology of a lesion showed a subepidermal bulla with an eosinophilic infiltrate and trace IgG was observed at the dermoepidermal junction by direct IF. When referred to University of Southern California, she was on 60 mg of prednisone per day and her indirect IF and ELISA results were negative. Because of the