CASE SERIES

Increasing evidence for omalizumab in the treatment of bullous pemphigoid

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INTRODUCTION

Bullous pemphigoid (BP) is an acquired autoimmune blistering disease characterized by the formation of autoantibodies against hemidesmosomal antigens BP180 and BP230. Although IgG autoantibodies predominate within the plasma and skin of BP patients, some features of the disease cannot be explained solely by IgG-mediated mechanisms.1,2 IgE autoantibodies are also detectable in at least 75% of untreated BP patients and autoreactive IgE-mediated inflammation has been shown to contribute to the pathogenesis of BP.1,2

Given the multiple immunologic mechanisms thought to be at play in the pathogenesis of BP, omalizumab, a humanized monoclonal antibody against IgE, has emerged as a novel treatment alternative. To date, omalizumab has been viewed largely as an adjunctive therapy for refractory cases or cases in which more aggressive immunosuppressive therapy is contraindicated. Here we report the largest case series to date evaluating use of omalizumab for BP, providing novel insight into this therapeutic option and further support for its use in the treatment of BP.

METHODS

After approval from the institutional review board at the University of California Los Angeles, we performed a retrospective chart review of patients treated at a single academic institution over a 32-month period from April 2016 to December 2018. All patients with a diagnosis of BP who were treated with omalizumab during this timeframe were included in the analysis. Data were obtained through comprehensive review of pathology reports, laboratory data, and physician documentation. Standard descriptive statistics and nonparametric analysis were performed on the data.

RESULTS

Eleven patients were included in the analysis, with a median age of 78 years. All 11 patients underwent biopsies, most of which found subepidermal bullae with eosinophils (Table I). Direct immunofluorescence (DIF) was performed in 8 cases (72.7%), with 6 of 8 (75.0%) showing linear staining along the basement membrane zone and 1 showing patchy staining along basement membrane zone. DIF in the eighth case was performed by an outside provider and was not available for review. Indirect immunofluorescence (IIF) was performed in 7 cases (63.6%), with 6 of 7 (85.7%) showing positive staining on the epidermal side of salt-spit skin.

Enzyme-linked immunosorbent assay (ELISA) was performed in 10 patients (90.9%) prior to starting omalizumab; BP180 (BPAG2) was elevated in 10 of 10 (100.0%). Total serum IgE levels were elevated in 10 of 11 patients (90.9%) prior to starting omalizumab, and 4 of 11 patients (36.4%) had elevated serum

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### Table I. Diagnostic studies

| Patient no. | Hematoxylin-eosin | DIF | IF | BP180 ELISA (nl: 1-9) | BP230 ELISA (nl:1-14) | Baseline IgE (nl:<100) | Peak Abs Eos (<0.5 × 10^9/µL) |
|-------------|-------------------|-----|----|------------------------|------------------------|------------------------|-------------------------------|
| 1 | Subepidermal blister with numerous eosinophils | 2+ IgG, C3, and IgM in a homogenous, linear pattern along basement membrane zone | N/A | 70.2 | <5 | 592 | 5.9 |
| 2 | Subepidermal bulla/cleft with numerous neutrophils and eosinophils | 1+ C3 in a homogeneous, linear pattern along basement membrane zone | Basement membrane zone antibody positive, titer 1:2560 | 197 | 132 | 427 | 0.19 |
| 3 | Spongiosis, focal vesiculation, and heavy eosinophilia | 1+ C3 in a patchy pattern along dermal-epidermal junction | Positive human split skin IgG, epidermal pattern | 40.7 | <5 | 328 | 0.33 |
| 4 | Subepidermal split with eosinophils | N/A | N/A | 193 | 10 | 4480 | 0.17 |
| 5 | Subepidermal blister with numerous eosinophils | 2+ IgG and C3 in a linear pattern along dermoeipidermal junction; spotty 1+ granular IgM along dermoeipidermal junction | Positive human split skin IgG, epidermal pattern, titer >1:40,960 | N/A | N/A | N/A | 3.01 |
| 6 | Cell-poor subepidermal blister | 2+ linear IgG and C3 staining along basement membrane zone | Positive human split skin IgG, epidermal pattern, titer 1:640 | 12 | 1 | 1121 | 0.12 |
| 7 | Report not available | N/A | N/A | 96 | 21 | 607 | N/A |
| 8 | Subepidermal bullous formation with numerous perivascular eosinophils and epidermal spongiosis | C3 and IgG in a linear pattern along basal layer of epidermis | N/A | 175 | 3 | 5388 | 0.71 |
| 9 | Subepidermal bullae including several eosinophils | Report not available | Positive human split skin IgG (titer 1:640) and IgA (titer 1:20), epidermal-dermal combined pattern, epidermal predominant | 159 | 1 | 2424 | 0.64 |
| 10 | Subepidermal and subcorneal blister containing few neutrophils | N/A | Positive human split skin IgG, epidermal pattern; titer 1:10,240 | 21.9 | 51.9 | 402 | 0.05 |
| 11 | Subepidermal bullous dermatosis with numerous eosinophils and eosinophilic spongiosis | 1-2+ IgG and C3 in a homogenous, linear pattern along basement membrane zone | Positive human split skin IgG, epidermal pattern; titer 1:20,480 | 27 | 87 | 2446 | 0.02 |

N/A, Not applicable.
| Patient no. | Age | Sex | Fitzpatrick skin type | Involved site(s) | Therapies prior to omalizumab | Concurrent therapies at any point while on omalizumab | Omalizumab dose | Maximum prednisone dose prior to omalizumab (mg) | Prednisone dose at omalizumab initiation (mg) | Lowest prednisone dose while on omalizumab (mg) | % BSA lowest during treatment | % BSA highest during treatment | Category of overall response |
|------------|-----|-----|-----------------------|------------------|-------------------------------|-----------------------------------------------------|----------------|-----------------------------------------------|----------------------------------------------|-----------------------------------------------|-------------------------------|-------------------------------|-------------------------------|
| 1          | 80  | F   | 1                     | Head/neck, trunk, extremities | Prednisone, doxycycline, azathioprine, rituximab, * class 1 topical steroids | Prednisone, doxycycline, azathioprine | 375 mg q2 weeks | 60                                           | 20                                          | 0                                      | 50                             | 0                             | 81 | Full |
| 2          | 82  | F   | 4                     | Trunk, extremities | Prednisone, doxycycline, class 1 topical steroids | Prednisone, doxycycline, class 1 topical steroids | 300 mg q4 weeks | 30                                           | 5                                           | 0                                      | 10                             | 0                             | 9 | Full |
| 3          | 76  | M   | 1                     | Trunk                | Prednisone, doxycycline, class 1 topical steroids | Prednisone, class 1 topical steroids | 300 mg q4 weeks | 60                                           | 7.5                                         | 0                                       | 10                             | 0                             | 5 | Full |
| 4          | 88  | M   | 2                     | Trunk, extremities | Prednisone, doxycycline | Prednisone, doxycycline | 300 mg q4 weeks | 40                                           | 20                                          | 2.5                                   | 15                             | 0                             | 9 | Full |
| 5          | 76  | F   | 1                     | Extremities         | Prednisone, doxycycline, niacinamide, class 1 topical steroids | Doxycycline, niacinamide, class 1 topical steroids | 300 mg q4 weeks | 5                                            | 0                                           | 0                                       | 30                             | 0                             | 0 | Full |
| 6          | 67  | M   | 4                     | Head/neck, trunk, mucosa, extremities | Prednisone, doxycycline, MMF, † class 1 topical steroids | Prednisone, MMF, doxycycline, class 1 topical steroids | 300 mg q4 weeks | Unknown (outside provider) | 10                                          | 0                               | 90                             | 50                            | 90 | Partial |
| 7          | 81  | M   | 2                     | Trunk, extremities | Prednisone, class 1 topical steroids | Prednisone, class 1 topical steroids | 300 mg q4 weeks | >60 (outside provider) | 20                                          | 2.5                                   | 36                             | 20                            | 36 | Partial |

* Indicates rituximab use discontinued after first 4 weeks.
† Indicates MMF use discontinued after first 4 weeks.
| Case | Age | Gender | Extremities | Medications | Prednisone | Duration | Improvement |
|------|-----|--------|-------------|-------------|------------|----------|-------------|
| 8    | 57  | F      | Head/neck, trunk, extremities | Prednisone, class 1 topical steroids | 300 mg q4 weeks | 80 15 15 54 54 76 | None |
| 9    | 74  | M      | Head/neck, trunk, extremities | Prednisone, doxycycline, niacinamide, class 1 topical steroids | 300 mg q4 weeks | 80 80 20 60 60 60 | None |
| 10   | 85  | M      | Trunk, extremities | Prednisone, IVIG, class 1 topical steroids | 300 mg q4 weeks | Unknown (outside provider) | Full |
| 11   | 95  | F      | Trunk, extremities | Prednisone, doxycycline, niacinamide, class 1 topical steroids | 300 mg q4 weeks | 20 20 5 5 <5 <5 | Partial |

**Notes:**
- *IVIG, Intravenous immunoglobulin; MMF, mycophenolate mofetil.
- *Continued to have severe active disease despite azathioprine and rituximab; therefore, omalizumab was initiated 5 months after last dose of rituximab.
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absolute eosinophils prior to omalizumab (Table I). Based on nonparametric analysis (Kruskal-Wallis test), there was no significant difference in IgE levels among full, partial, and nonresponders to treatment ($P = .15$). Similarly, nonparametric analysis found no significant difference in absolute eosinophil levels among full, partial, and nonresponders ($P = .16$).

All 11 patients were treated with prednisone prior to receiving omalizumab, and 8 patients had previously received another systemic medication (Table II), including 1 patient who was treated with rituximab 5 months prior to omalizumab initiation. Taken together, patients in this cohort did not respond to a mean of 2.3 systemic agents prior to initiation of omalizumab. The median duration of disease prior to initiation of omalizumab was 206 days or 6.8 months (range, 33-584 days). Ten of 11 patients (90.9%) were treated with a dosing regimen of 300 mg every 4 weeks, and a single patient was treated with a regimen of 375 mg every 2 weeks.

At the time of analysis, 6 of 11 patients (54.5%) experienced complete clearance of skin lesions after a median duration of 4.4 months on omalizumab (Table II). Time to complete clearance ranged from less than 1 month to 5.9 months. All 10 patients on prednisone at the time of omalizumab initiation were able to reduce the dose of prednisone, and 5 of 10 patients (50.0%) were able to discontinue systemic steroids completely. Three of 11 patients (27.3%) had a partial response to omalizumab. Among these partial responders, one patient was improving but was hospitalized for influenza complicated by bacterial superinfection and aspiration pneumonia. That patient subsequently died. The second was also improving after receiving 2 injections at the time of analysis. The third had overall improvement with a decrease in affected body surface area (BSA) from 90% to 50% and decreased prednisone requirement; however, the patient still had a significant burden of disease and remained on mycophenolate mofetil in addition to omalizumab. The remaining 2 patients did not respond to treatment and experienced recalcitrant flares while on omalizumab. Interestingly, one nonresponder reported repeated flaring of skin lesions 2 to 3 days after omalizumab injections, so the medication was discontinued. The median duration of treatment in all patients at the time of analysis was 12.6 months.

**DISCUSSION**

Although omalizumab is increasingly being recognized as a potential alternative agent in the treatment of BP, evidence to support this practice remains limited. Fairley et al. reported the first case of BP treated with omalizumab in a patient with adverse effects to chronic corticosteroid use. Since then, a handful of other cases of successful treatment of BP with omalizumab have been reported. In a small study by Yu et al., 5 of 6 patients fully responded to omalizumab as a monotherapy or in combination with traditional agents. This report represents the largest case series to date evaluating use of omalizumab for BP, significantly increasing the number of documented cases in the literature.

Omalizumab was well tolerated without adverse effects in 9 of 11 patients (81.8%). One patient experienced possible omalizumab-induced BP flares, which required discontinuation of the medication. This potential adverse effect has not been reported previously and merits further investigation. One patient died from infection while on omalizumab therapy with prednisone. The remaining 10 patients did not experience serious or life-threatening side effects associated with omalizumab, which is significant when comparing the risk profile of this medication to other commonly used systemic agents for BP.

Omalizumab appears to have a significant disease-modifying effect in most treated patients, as evidenced by percentage decrease in BSA involvement as well as ability to reduce or discontinue treatment with prednisone. All patients receiving systemic steroids at the time of omalizumab initiation tolerated lowering of their steroid dosage without disease flare and 50% were able to discontinue steroids completely. This is particularly noteworthy since BP primarily affects older patients, many of whom have significant side effects from long-term systemic steroid use. In our cohort, 7 of 11 patients (63.6%) experienced adverse effects likely related to prednisone. These included spinal and femoral fractures, osteoporosis, severe hyperglycemia, hypertension, and facial and leg swelling.

Baseline serum IgE and eosinophil levels did not predict treatment response, suggesting that patient selection for omalizumab should not hinge on these laboratory values. Most patients in this cohort were treated with 300 mg of omalizumab every 4 weeks, the approved dosing for chronic idiopathic urticaria. Given tolerability and positive treatment response, this may be a reasonable dosing regimen for initial prospective studies for BP.

Two patients in this series discontinued omalizumab because of issues with financial access to the medication. The first of these patients had flaring of his disease within months of stopping omalizumab but fortunately was able to restart the medication through a medication assistance.
program. The second patient had to be bridged to an alternate systemic immunosuppressive therapy and maintained disease control. Medication cost and insurance coverage, along with the requirement for patients to be monitored after each injection due to a rare risk of anaphylactic reactions, may represent the greatest barriers to more widespread use of omalizumab by dermatologists.

This case series study has several limitations. Importantly, there is no control group, which would have allowed for direct comparative assessment of the effects of omalizumab on patient outcomes. Although this is the largest case series to date evaluating omalizumab for the treatment of BP, the sample size is small, and all patients were treated at a single academic institution. Finally, given the retrospective nature of this review, laboratory tests such as DIF, IFF, ELISA, IgE, and eosinophil levels were available for most but not all patients.

The positive treatment responses reported in this series are in line with the findings of previous smaller reports, reinforcing the potential value of larger, prospective studies to optimize treatment protocols and delineate which patients will benefit most from omalizumab.

REFERENCES
1. Fania L, Caldarola G, Müller R, et al. IgE recognition of bullous pemphigoid (BP)180 and BP230 in BP patients and elderly individuals with pruritic dermatoses. Clin Immunol. 2012;143(3): 236-245.
2. Messingham KA, Holahan HM, Fairley JA. Unraveling the significance of IgE autoantibodies in organ-specific autoimmunity: lessons learned from bullous pemphigoid. Immunol Res. 2014;59(1-3):273-278.
3. Fairley JA, Baum CL, Brandt DS, Messingham KA. Pathogenicity of IgE in autoimmunity: successful treatment of bullous pemphigoid with omalizumab. J Allergy Clin Immunol. 2009;123(3):704-705.
4. Yu KK, Crew AB, Messingham KAM, Fairley JA, Woodley DT. Omalizumab therapy for bullous pemphigoid. J Am Acad Dermatol. 2014;71(3):468-474.