

SHORT REPORT

Successful treatment of bullous pemphigoid with omalizumab as corticosteroid-sparing agent: report of two cases and review of literature

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Abstract

Background Bullous pemphigoid (BP) is an autoimmune blistering disease that is characterized by formation of subepidermal bullae due to functional disturbance of the hemidesmosomal proteins on the keratinocytes at the basal membrane zone. In recent years, several studies have emphasized the important role of IgE autoantibodies in the pathogenesis of BP. Consequently, a therapeutic approach using IgE depleting antibodies, such as a humanized monoclonal anti-IgE antibody (e.g. omalizumab) may represent a new option for treatment of this autoimmune disease.

Methods In this paper, we report about the successful treatment of BP with omalizumab in two patients and provide a review of the current literature on the relationship between IgE antibodies and this autoimmune blistering disease.

Results Two patients with therapy-resistant BP were treated with humanized monoclonal anti-IgE antibody omalizumab 300 mg subcutaneously every 3 weeks as corticosteroid-sparing agent. Under this therapy, both patients experienced a significant improvement of skin condition and almost complete resolution of pruritus. The treatment was well tolerated.

Conclusion Until recently IgG autoantibodies against the basal membrane proteins BP180 und BP230 were considered to be causative in the pathogenesis of BP. However, new *in vitro* studies as well as data from experimental mouse models have indicated that in addition to specific IgG, also IgE antibodies against BP180 and BP230 play a role in the development of this disease. Based on these new findings, new treatment modalities of BP became possible.

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Introduction

Bullous pemphigoid (BP) is an autoimmune blistering disease with rising prevalence in the elderly population. Its incidence varies between 7 and 43 per million per year in different parts of Western Europe,^{1–4} the mean age of the onset is around 74–80 years, but also younger patients may be affected.^{1,2,5} There are numerous therapeutic options available. Several national and international guidelines have been already published, and, depending on comorbidities of the patients, effectively guide the choice of therapy.^{6–8} The standard therapies consist of topical

and systemic corticosteroids, and other immunosuppressive agents like azathioprine, mycophenolate mofetil, dapsone, methotrexate, anti-inflammatory antibiotics (e.g. tetracyclines), or sulfonamides, furthermore intravenous immunoglobulins, cyclophosphamide and rituximab are also reported to be effective in therapy-resistant cases.

In recent years, several studies have emphasized the importance of IgE autoantibodies for the pathogenesis of BP.^{9–17} Consequently, a therapeutic approach using IgE depleting antibodies, such as a humanized monoclonal anti-IgE antibody omalizumab may represent a new option for treatment of this autoimmune disease. Herein, we report about the successful treatment of BP with omalizumab as corticosteroid-sparing agent in two patients and provide a review of the current

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literature on the increasingly recognized role of IgE antibodies in the pathogenesis and the therapeutic success of omalizumab for therapy-refractory cases of this autoimmune blistering disease.

Case 1

A 40-year old female patient was referred to our department with newly diagnosed BP. Histological examination of the biopsies of lesional skin revealed subepidermal blisters. Direct immunofluorescence (DIF) of perilesional skin showed linear deposition of IgG at the dermal–epidermal junction. Also, circulating serum IgG autoantibodies targeting BP180 and BP230 antigens could be identified by Enzyme-Linked Immunosorbent Assay (ELISA). The patient was suffering from hypothyroidism, vitiligo and obesity (BMI 27.7). We started an oral immunosuppressive therapy with prednisolone 0.5 mg/kg bodyweight/day (40 mg/day) together with azathioprine (100 mg/day). Under this therapy, the patient reported partial remission with subsequent tapering of oral prednisolone. Six months later, the patient experienced urinary sepsis requiring intensive care hospitalization; thus, discontinuation of systemic immunosuppressive therapy was decided. Eight weeks after the withdrawal of prednisolone and azathioprine, the patient experienced a severe relapse of BP. We reinitiated therapy with prednisolone 0.5 mg/kg bodyweight/day (40 mg/day) and azathioprine (100 mg/day). After 4 weeks of treatment, however, the patient continued to develop new blisters and reported continued severe pruritus even upon increase of prednisolone to 1 mg/kg bodyweight/day (80 mg/day). Overall 12 weeks after restart of the therapy, the patient still developed new skin lesions and suffered from disabling itching (Fig. 1a). In addition, due to excessive weight gain (10 kg in 12 weeks) the patient wished to avoid further treatment with high dose systemic prednisolone.

We discontinued azathioprine and introduced systemic therapy with omalizumab 300 mg subcutaneously every 4 weeks with subsequent reduction of systemic prednisolone from the initial dose of 60 mg/day. Five days after the first dose of omalizumab, the patient reported improvement of pruritus, followed by reduction in lesion counts over the next weeks. However, the patient described repeatedly increasing number of skin lesions 1 week before due time of the next omalizumab injection, thus injection intervals were decreased to 3 weeks. Concomitantly, we could reduce systemic prednisolone to daily doses of 5 mg after the fourth dose of omalizumab. Till the present time the patient has received 20 injections of omalizumab over 15 months and is on 5 mg/day prednisolone. She is free of pruritus and keeps having few isolated blisters (Fig. 1b). No side-effects were noted.

During the therapy with omalizumab, we did not observe significant changes of circulating autoantibody titres (specific IgG against BP180 and BP230 as determined by ELISA). However, total IgE level dropped (from 1697 kU/L before treatment to 1028 kU/L after 8 injections) (Table 1).

Case 2

A 63-year-old male patient was referred to our department with severe pruritus, erythematous plaques and skin erosions for at least 6 months. He suffered from obesity (BMI > 30), hypertension, diabetes mellitus type II, hypercholesterolemia and also mild allergic rhinitis due to pollen allergy. We diagnosed BP detecting linear deposition of IgG at the dermal–epidermal junction by DIF of perilesional skin and circulating serum IgG autoantibodies targeting BP180 and BP230 antigens using ELISA, and started treatment with oral prednisolone at 0.5 mg/kg bodyweight/day (40 mg/day). The symptoms of BP

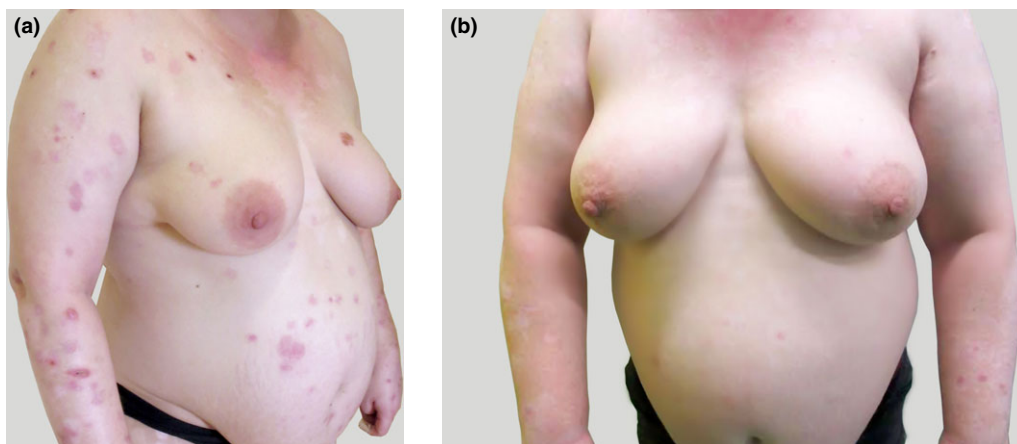


Figure 1 Clinical presentation of patient 1 before and during systemic therapy with omalizumab 300 mg s.c. every 3 weeks and prednisolone 5 mg/day p.o. (a) Persisting lesions on the abdomen and arms during systemic therapy with 60 mg/day prednisolone and 100 mg/day azathioprine p.o. (b) 24 weeks after the introduction of omalizumab, complete resolution of erosions and blisters was achieved, post-inflammatory hyperpigmentations and occasional scars are seen.

Table 1 Clinical and serological parameters of the patients before and during therapy with omalizumab 300 mg s.c. every 3 weeks (after 8 injections): in patient 1 in combination with prednisolone 5 mg/day and in patient 2 as a monotherapy.

	BPDAI		BPDAI pruritus component		Eosinophilic granulocytes (%)		Total IgE (kU/L)		BP180 -specific IgG (ELISA) (U/mL)		BP230 -specific IgG (ELISA) (U/mL)	
	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy
Patient 1	51	7	27	3	5.5	5.1	1697	1028	121.7	165.3	46.5	36.2
Patient 2	38	3	22	3	11	3.4	1074	1873	412.5	259.1	112.2	61.3

The Bullous Pemphigoid Disease Area Index (BPDAI) (with a total maximum score of 372) and BPDAI pruritus component based on a visual analogue scale (with a total maximum score of 30) were calculated according to the recommendations of the International Pemphigoid Committee.

improved, but the therapy led to severe side-effects (worsening of hypertension, increased blood glucose levels and excessive weight gain) (Fig. 2a).

We decided to start systemic therapy with omalizumab 300 mg subcutaneously every 3 weeks. Subsequent to the first injection, the patient reported resolution of pruritus within few days. We reduced oral prednisolone from initially 40 mg/day tapering by 5 mg every week, and after the third dose of omalizumab systemic corticosteroids were stopped without further exacerbation of BP (Fig. 2b).

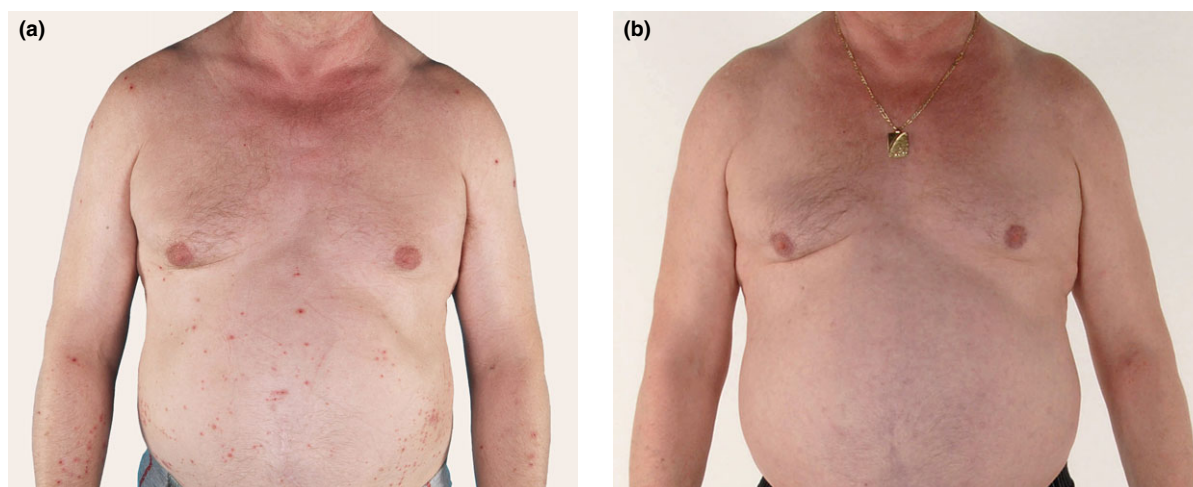
Overall, the patient received eight courses of omalizumab and was almost free of symptoms and completely free of side-effects during the therapy. We had to stop the therapy due to health insurance problems. About 8 weeks after discontinuation of omalizumab therapy, the patient developed exacerbation of the disease with severe pruritus and new skin lesions, so we had to reintroduce oral prednisolone.

Unlike the first case, autoantibody titres dropped (BP180 and BP230-specific IgG as determined by ELISA) during the therapy with omalizumab, but remained elevated. The eosinophilic

granulocytes dropped (from 11% before treatment with omalizumab to the normal level of 3.4% after eight injections), but the total IgE count in serum remained elevated (with 1074 kU/L before treatment with omalizumab and 1873 kU/L after eight injections) (Table 1).

Discussion and review of literature

BP is an autoimmune subepidermal blistering disease characterized by formation of tense bullae of the skin due to the functional disturbance of the hemidesmosomal proteins within the cutaneous basal membrane zone (BMZ). Two main autoantigens have been identified, BP230 (BPAg1) and BP180 (BPAg2, collagen XVII). The gold standard for the diagnosis is DIF from perilesional skin, demonstrating a linear deposition of IgG along the BMZ. Also IgG autoantibodies targeting the two main autoantigens can be detected in the patients' sera via ELISA.⁶⁻⁸ Thus, previously IgG autoantibodies have been considered to be the major players in the pathogenesis of BP. Nevertheless, elevation of total IgE in sera of BP patients occurs frequently.^{5,9,10} Consequently, IgE antibodies targeting NC16A domain of

**Figure 2** Clinical presentation of patient 2 before and during systemic therapy with omalizumab 300 mg s.c. every 3 weeks. (a) Recurrent skin lesions at the abdomen under therapy with prednisolone 40 mg/day. (b) 12 weeks after the introduction of omalizumab, complete resolution of the lesions with occasional post-inflammatory hyperpigmentations.

BP180 protein have been identified.^{11–13} Messingham *et al.* developed a highly specific and sensitive ELISA to detect NC16A-specific circulating IgE autoantibodies, which were identified in up to 77% of BP sera.¹⁴ Moreover, linear deposits of IgE autoantibodies along the dermal–epidermal junction were detectable in 41% of the patients.¹⁵

These findings suggest an important role of IgE antibodies in the pathogenesis of BP, which could be subsequently proved to be pathogenic using a murine model of BP. Zone *et al.* used severe combined immunodeficiency mice with engrafted human skin and injected them subcutaneously an IgE hybridoma producing specific IgE antibodies to LABD97, a component of the shed ectodomain of BP180. Histologically, the mice developed intense eosinophil infiltration and degranulation of human mast cells within the grafts, and most of the animals developed histologically, but not clinically visible, subepidermal blisters.¹⁶ Fairley *et al.* investigated another murine model of BP. Here, total IgE antibodies isolated from sera of BP patients and healthy controls were injected into human skin grafted to athymic, nude mice. Twenty-four hours after injection, erythematous, elevated plaques were observed in all human skin grafts receiving IgE from BP patients. Histologically significant dermal infiltrate of partly degranulated neutrophils, eosinophils and mast cells were seen.¹⁷

Reflecting about current findings on the pathogenesis of BP, Messingham *et al.* proposed the mechanism of action of IgE autoantibodies in BP. According to Messingham's hypothesis, IgE autoantibodies bind to the surface of cutaneous mast cells via the high affinity IgE receptor, FcεRI. Binding of the antigenic NC16A domain of BP180 to IgE causes receptor cross-linking and mast cell degranulation with subsequent release of mediators including histamine, cytokines and proteases. Consequently, an immune cascade is triggered, recruiting additional effector cells (e.g. eosinophils and neutrophils) resulting in further destruction of the BMZ.¹⁸ Alternatively, free IgE autoantibodies can bind via their variable region directly to NC16A expressed by basal keratinocytes. Binding of IgE autoantibodies to keratinocyte BP180 results in antibody internalization ensued by the release of the pro-inflammatory cytokines IL-6 and IL-8. It was observed *in vitro* that the direct effects of IgE autoantibodies contribute to inflammation and fragility of the BMZ.^{18,19} Taken together, these two outlined mechanisms are thought to contribute to the degradation of the BMZ in BP.

Based on these recent aspects of the pathogenesis of BP, a new option of anti-IgE therapy becomes evident. Omalizumab is a humanized monoclonal anti-IgE antibody. It targets the receptor-binding site on circulating IgE and inhibits the binding of IgE to its receptors on effector cells by formation of IgE–anti-IgE immune complexes.²⁰ It is also known to decrease the expression of IgE receptors, FcεRI, on immune effector cells;²¹ thus, the effect of IgE antibodies is neutralized.

Using these benefits of anti-IgE treatment, a number of case reports and small case series have been published on treatment

of BP with omalizumab in recent years. Altogether, 10 BP patients have been reported to receive therapy with omalizumab (different doses) with altogether good results and lack of side-effects.^{22–26} Because of the small number of patients treated, it is difficult to make a conclusion about the appropriate therapy regimen. It is also not possible to predict, which patients could benefit from anti-IgE therapy. Thus, our current report on the successful treatment of two patients with therapy-resistant BP with omalizumab alone, or in combination with low doses of oral corticosteroids gives further credential to a potential randomized study. Further investigation and better understanding of the role of IgE antibodies in BP may result in the clinical development of better therapies of this autoimmune blistering disease in the future.

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