

DR. DIPANKAR DE (Orcid ID : 0000-0001-8682-2598)

DR. AKANKSHA KAUSHIK (Orcid ID : 0000-0001-5461-2465)

DR. RAHUL MAHAJAN (Orcid ID : 0000-0003-4320-3193)

PROF. ENNO SCHMIDT (Orcid ID : 0000-0002-1206-8913)

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Title: Omalizumab: an underutilized treatment option in bullous pemphigoid patients with co-morbidities

Authors: Dipankar De¹, MD, Akanksha Kaushik¹, MD, Sanjeev Handa¹, MD, FAMS, FRCP (Edinburgh), Rahul Mahajan¹, MD, MNAMS, Enno Schmidt, MD, PhD^{2,3}

Affiliations

¹Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

²Department of Dermatology, University of Lübeck, Lübeck, Germany

³Lübeck Institute of Experimental Dermatology (LIED), University of Lübeck, Lübeck, Germany

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Corresponding Author:

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Dr Dipankar De

Additional Professor, Department of Dermatology, Venereology, and Leprology,
Postgraduate Institute of Medical Education and Research, Chandigarh, India

Phone no: +91-172-2756562

Fax No: +91-172-2744401

Email: dr_dipankar_de@yahoo.in

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Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disorder commonly affecting the elderly in the age group of 60-80 years.¹ IgG autoantibodies against the hemidesmosomal proteins BP180 and BP 230 have been deemed central in pathogenesis. However, IgE also appears to be important in pathogenesis and targeting IgE autoantibodies may be an interesting and effective treatment option. Elevated serum levels of anti-BP180 and anti-BP230 IgE have been observed in 40-77% of BP patients and anti-BP180 IgE serum levels have shown correlation with disease activity.² By direct IF microscopy, IgE deposits have been found in the upper dermis localized on mast cells and/or eosinophils.³ It was observed that patients with IgE deposits along the dermal-epidermal junction had a higher Bullous Pemphigoid Disease Area Index (BPDAI) score compared to patients without linear IgE deposits.⁴ A direct pro-inflammatory effect of IgE on BMZ has also been proposed. Insights to a functional relevance of anti-BP180 IgE came from the findings of increased IL-6 and IL-8 release from cultured keratinocytes upon incubation with anti-BP180 IgE and dependence of anti-BP180 IgE on eosinophils for induction of blister formation in mice.⁵

Immunosuppressants like topical and systemic corticosteroids are considered mainstay of therapy in BP but their side effect profile, precludes use for longer durations in many elderly patients.⁶ Omalizumab, an anti-IgE monoclonal antibody, is an established agent in the management of allergic asthma and has a favourable adverse effect profile. Following a published case report in 2009,⁷ a few other reports have shown encouraging results with omalizumab use in BP.⁸⁻¹⁰ We describe here the safety and effectiveness of omalizumab in six BP patients with severe disease, significant pruritic symptoms and associated co-morbidities in an Indian setting. BP patients attending the autoimmune bullous disease clinic of Postgraduate Institute of Medical Education and Research, Chandigarh, India, between September 2018 to October 2019, with severe disease, pruritus and showing either inadequate response or having contraindication to systemic corticosteroids were treated with omalizumab (300 mg) subcutaneous injections, every 4 weeks. They were followed-up every month and omalizumab injection(s) beyond 3-months (12 weeks) was individualized for each patient based upon clinical response and financial affordability. The mean follow-up period was 16.67 weeks (range 12-20 weeks). BPDAI was assessed at baseline and at each follow-up visit. Anti-BP180 and BP230 antibody titres were measured using ELISA (Euroimmun AG, Germany) following manufacturer's protocol at baseline and at 12 weeks. Qualitative IgE anti-BP180 and BP230 was also carried out at baseline and at 12 weeks. The

clinico-demographic details, comorbidities, previous treatment received and response to treatment, treatment with omalizumab, other concurrent treatments and response to omalizumab in our 6 patients is presented in Table 1. Omalizumab used in our patients resulted in significant improvement of pruritic symptoms, re-epithelialisation was observed in 4 to 6 weeks in all cases, and BPDAI scores showed consistent improvement on follow-up (Figure 1). The drug was well-tolerated and no adverse effects were reported.

The effects observed in our patients suggest that omalizumab is a well-tolerated and effective treatment option in BP patients with co-morbidities that preclude use of corticosteroids or other immunosuppressive agents. In addition to clinical effectiveness, other benefits of use of omalizumab in elderly BP patients are non-requirement of monitoring investigations, lack of side effects, and subcutaneous injections that can be carried out at home. The fact that 4 patients had no circulating anti-BP180 or anti-BP230 IgE at baseline but showed significant clinical improvement and reduction of IgG anti-BP180 and anti-BP230 serum levels upon treatment with omalizumab is intriguing. Our study had some limitations, including a relatively small sample size, being a single-centre study and not having a control group. Future randomized controlled trials are needed to establish omalizumab as effective and safe treatment option for BP patients and to determine which patient subset benefits most from anti-IgE therapy.

Legends to figures

Figure 1a: A 62-year-old female with bullous pemphigoid at presentation; Figure 1b: Same patient showing improvement in skin lesions after treatment with omalizumab at 4 weeks follow-up.

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Table 1: Detailed characteristics of patients with BP treated with omalizumab

S. No.	Age (in years)/ Sex	Disease duration (in months)	Treatment received in the past	Co-morbidities	Baseline IgE (U/ ml)	BPDAI scores		IgE antiBP180/ IgE anti BP230		Number of four-weekly omalizumab injections received in first 12 weeks	Number of four-weekly omalizumab injections received beyond 12 weeks	Concurrent therapy given with omalizumab	Clinical Response to therapy	Follow-up period	Systemic steroid use on follow-up
						Baseline	12 weeks	Baseline	12 weeks						
1	62/ F	3	Topical & oral corticosteroids	T2DM Chronic kidney disease	1151	58	24	Negative/negative	Negative/negative	3	0	Antihistamines Topical clobetasol 0.05%	Significant improvement	16 weeks	No
2	85/ F	2.5	Topical & oral corticosteroids Antihistamines	T2DM; on sitagliptin (100 mg/day), HTN	409	51	6	Negative /negative	Negative/negative	3	1	Antihistamines Oral prednisolone ¶	Significant improvement	16 weeks	Yes ¶
3	59/ M	9	Oral steroids Antihistamines	T2DM; on sitagliptin (100 mg/day) since 1 month, HTN, ischemic heart disease (CABG done) Hypothyroidism	22682	34	15	Negative/positive	Negative/positive	3	2	Antihistamines Topical clobetasol 0.05% Oral prednisolone ¶¶	Significant improvement	16 weeks	Yes ¶¶
4	58/ F	5	Oral steroids	T2DM Chronic kidney disease Hypothyroidism	21630	20	11	Positive/positive	Positive/negative	3	0	Antihistamines Topical clobetasol 0.05%	Significant improvement	12 weeks	No
5	62/ F	2.5	Dapsone Antihistamines Antibiotics	Seropositive for hepatitis B	4217	42	19	Positive/negative	Positive /negative	3	0	Antihistamines	Significant improvement	20 weeks	No

6	61/ M	6	Oral steroids	HTN, Ischemic heart disease (CABG done)	133	42	16	Negative/negative	Negative/negative	3	3	Antihistamines Oral prednisolone [¶]	Significant improvement	20 weeks	Yes ^{¶¶}
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Abbreviations: M: Male; F: Female; T2DM: Type 2 Diabetes Mellitus; HTN: hypertension; CABG: Coronary artery bypass grafting

¶: Prednisolone dose reduced to 20 mg/day

¶¶: Prednisolone dose reduced to 10 mg/day

