An IgE-independent response to dupilumab in refractory bullous pemphigoid?

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Background:

Bullous pemphigoid (BP) is a common autoimmune blistering disease characterized by the formation of tense, pruritic subepidermal bullae [1]. Pathogenesis of the disease involves immunoglobulin G (IgG) and E (IgE) autoantibodies targeting the hemidesmosome structures BP180 and BP230. BP can be debilitating and has a high mortality rate. [2] The Th2 cytokines interleukin-4 (IL-4) and IL-13 are central to its pathogenesis, recruiting eosinophils and stimulating B-cells to produce autoantibodies.[3] Due to its dual inhibition of IL-4 and IL-13 signaling, dupilumab, a recombinant IgG4 monoclonal antibody, has been investigated as a treatment option for steroid-refractory BP. [4]

Clinical question:

Does pre-treatment serum IgE level correlate with response to dupilumab in refractory BP?

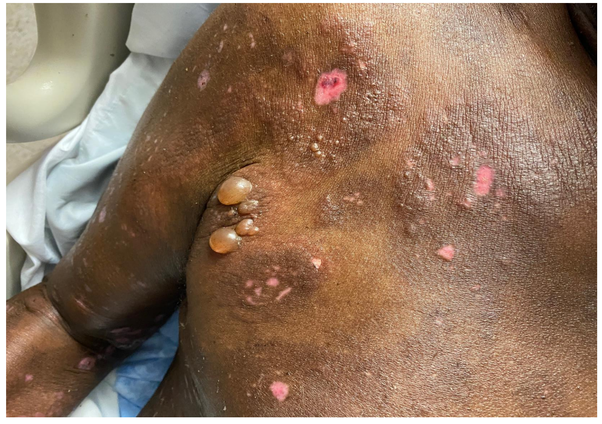
Cases:

We present a unique case series of two patients with biopsy proven BP, refractory to standard topical and oral therapies, who were successfully treated with dupilumab.

Patient 1 is a 73-year-old male who presented with severe BP and was subsequently admitted for hypernatremia and altered mental status. He did not respond to clobetasol ointment, doxycycline, and nicotinamide. A total serum IgE was obtained and resulted at >20,000 prior to initiation of therapy.

Patient 2 is a 98-year-old male with new diagnosis of BP who was initially treated with the same treatment regimen as patient 1, plus prednisone 40 mg daily with slow taper. A total serum IgE was obtained and resulted within normal limits.

Both patients were transitioned to dupilumab 600mg subcutaneous injection, followed by 300mg every 2 weeks with complete clearance of bullae and no significant pruritis after induction. Patient 2 did experience mild flares of disease with less than 8 bullae at a time and mild pruritus over time.



Urticarial plaques with tense bullae and erosions across the trunk in a 73 year old male with bullous pemphigoid.

Results:

	Patient 1	Patient 2
Age, sex	73, M	98, M
Prior therapies failed	Clobetasol ointment, doxycycline, niacinamide	Clobetasol ointment, doxycycline, niacinamide, prednisone 40mg daily with taper
Pre-treatment serum IgE	>20,000 (high)	Within normal limits
Post-induction serum IgE	12,000 (high)	Not obtained
Response at 3 months	Zero bullae No significant itch	Initial complete clearance of bullae; <8 breakthrough bullae occasionally thereafter; Mild itch

Conclusions:

- While dupilumab has been well described in case series as a novel and effective treatment for BP, to our knowledge, no literature has been published evaluating the role of patients' serum IgE levels on efficaciousness of dupilumab treatment.
- Traditionally, omalizumab, a monoclonal antibody against IgE, has been used for treatment of refractory BP in association with elevated IgE; however, our series suggests that dupilumab may be a more versatile option not only for patients with elevated IgE, but even those with normal levels.
- High dose oral steroids can have serious morbidity and mortality risk in the elderly population who have BP, so utilizing non-steroidal medications to effectively control this blistering condition is important.

Further directions and key takeaways:

- With the recent FDA approval of dupilumab for prurigo nodularis, there will be more opportunity to prescribe this medication for patients (e.g. pemphigoid nodularis).
- There is a need for continued investigation into optimal patient selection for dupilumab in refractory bullous pemphigoid, such as comparative studies that investigate the efficacy of omalizumab versus dupilumab in patients with elevated IgE.
- This limited case series suggests that dupilumab can be used successfully in refractory BP regardless of pre-treatment serum IgE level.

References:

1. Maglie R, Hertl M. Pharmacological advances in pemphigoid. Current Opinion in Pharmacology. 2019;46:34-43. doi:10.1016/j.coph.2018.12.007

2.Cortés B, Khelifa E, Clivaz L, et al. Mortality Rate in Bullous Pemphigoid: A Retrospective Monocentric Cohort Study. Dermatology. 2012;225(4):320-325. doi:10.1159/000345625

3.Russo R, Cozzani E, Gasparini G, Parodi A. Targeting interleukin 4 receptor α: A new approach to the treatment of cutaneous autoimmune bullous diseases? Dermatologic Therapy. 2020;33(1). doi:10.1111/dth.13190

4.Wang SH, Zuo YG. Commentary: Efficacy and Safety of Dupilumab in Moderate-to-Severe Bullous Pemphigoid. Front Immunol. 2021;12:800609. doi:10.3389/fimmu.2021.800609