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Journal

Dermatology Online Journal, 25(11)

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Publication Date

2019

DOI

10.5070/D32511046147

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Dupilumab for bullous pemphigoid with intractable pruritus

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Abstract

Bullous pemphigoid (BP) is an autoimmune blistering disorder that predominantly affects the elderly. Treatment regimens typically include topical and systemic immunosuppressive medications. Although effective, systemic corticosteroids are sometimes poorly tolerated in the elderly patient, contributing to the overall morbidity and mortality of BP. Dupilumab is a monoclonal antibody targeting interleukin 4 receptor alpha (IL4R α), approved for the treatment of atopic dermatitis, as well as moderate to severe asthma and chronic rhinosinusitis with nasal polyposis. In recent reports, dupilumab has been successfully used off-label to treat a variety of pruritic disorders, including chronic spontaneous urticaria [1], anal and genital itch [2], allergic contact dermatitis [3], and prurigo nodularis [4, 5]. We report here a case of an elderly patient with refractory BP whose symptoms of pruritus and blistering became well-controlled with the addition of dupilumab to the treatment regimen.

Keywords: dupilumab, bullous pemphigoid, pruritus, corticosteroid sparing, Th2 cytokines, IL4, IL13

Introduction

Bullous pemphigoid is an autoimmune blistering disorder characterized by antibodies targeting

hemidesmosomes at the dermal-epidermal junction (DEJ). In the acute setting, topical and systemic corticosteroids are typically the first-line treatments, which allow providers to bridge patients to corticosteroid sparing agents such as azathioprine, mycophenolate mofetil, or methotrexate. Given their low side effect profile, anti-inflammatories such as doxycycline and nicotinamide are often added to help control disease activity and can be effective when utilized alone in BP [6-9]. In refractory cases, biologic therapies such as rituximab [10-12] and omalizumab [13-17] have shown efficacy in a small number of cases. Dupilumab is a monoclonal antibody targeting IL4R α that reduces interleukin 4- and interleukin 13-mediated signaling [18]. It has been approved for the treatment of atopic dermatitis, as well as moderate to severe asthma and chronic rhinosinusitis with nasal polyposis. In recent reports, dupilumab has been successfully used off-label to treat a variety of pruritic disorders, including chronic spontaneous urticaria [1], anal and genital itch [2], allergic contact dermatitis [3], and prurigo nodularis [4, 5]. Herein, we report the use of dupilumab for BP in an elderly male with inadequately controlled pruritus despite concurrent topical corticosteroids, low/moderate dose systemic corticosteroids, doxycycline, nicotinamide, and mycophenolate mofetil.

Case Synopsis

An 89-year-old man with type 2 diabetes mellitus on metformin presented to our clinic with urticarial plaques and bullae despite 15 months of ongoing treatment with doxycycline 100mg twice daily, nicotinamide 500mg twice daily, mycophenolate mofetil 1000mg twice daily (peak of 1500mg twice daily), and prednisone 10mg daily. Prior skin biopsy showed spongiosis with focal epidermal vesicle formation and superficial dermal perivascular infiltrate containing eosinophils and lymphocytes. Direct immunofluorescence showed linear IgG and C3 deposition at the dermal-epidermal junction, consistent with the diagnosis of bullous pemphigoid. The patient was not on any medications suspected to be causing his BP. His treatment course was complicated by exacerbation of his type 2 diabetes mellitus, corticosteroid myopathy, and thrush. Although moderate doses of prednisone effectively reduced the severity of blistering lesions, his pruritus and diabetes were not sufficiently controlled. Attempts to very slowly taper his prednisone resulted in disease flares and severe pruritus. After two years, the patient complained of pill fatigue and concerns about prednisone and diabetes, thus a trial of omalizumab was initiated as an alternative corticosteroid sparing agent. He initially responded well, but experienced a disease flare 6 months after starting omalizumab. The patient elected to discontinue omalizumab owing to loss of efficacy. After a period off omalizumab, the patient was started on dupilumab. Within two weeks of starting dupilumab, the patient's pruritus markedly improved and at his 7-week follow up, his BP lesions had completely resolved. He is currently taking dupilumab every other week, prednisone 2.5mg daily, mycophenolate mofetil 500mg twice daily, doxycycline 100mg twice daily, and nicotinamide 500mg twice daily; he uses topical, clobetasol 0.05% cream as

needed. Our patient reported complete resolution of his pruritus after the first dose of dupilumab and continued benefit from the medication at one-year follow-up.

Case Discussion

Dupilumab is a human monoclonal antibody targeting IL4Ra that inhibits the signaling of Th2 cytokines, interleukin 4, and interleukin 13. It is currently approved for the treatment of atopic dermatitis, as well as moderate to severe asthma and chronic rhinosinusitis with nasal polyposis. Eosinophilic infiltration and production of Th2 cytokines are critical drivers of these diseases. Interestingly, studies have shown that eosinophils can contribute to the pathogenesis of BP by causing separation of the DEJ and driving anti-BP180 IgE-mediated skin blistering [19-25]. In addition, IL4 is essential for the initial recruitment of eosinophils, which promotes a positive feedback loop, contributing to further production of IL4 [26]. Expression of IL4 and IL13 in skin lesions [27] and a higher frequency of skin-homing cutaneous lymphocyte-associated antigen positive IL4 and IL13 producing T cells in skin blisters [28] further support the hypothesis that IL4 and IL13 are essential for BP disease pathogenesis. Release of eosinophilic granules may help explain the prominent pruritus observed in BP but not in other blistering disorders, which typically lack eosinophilic infiltration [26]. Pruritus without blisters can be the first presentation of BP [29]. The efficacy of dupilumab in successfully controlling this patient's pruritus may highlight a clinically relevant common Th2 pathway, which drives pruritus in both atopic dermatitis and BP. To our knowledge, there has been only one report of dupilumab for the treatment of BP in the literature [30]. This patient was also an elderly male with eosinophilic infiltration noted on biopsy who experienced substantial reduction in itching

after the first injection of dupilumab and resolution of blisters within the following weeks (**Table 1**). In the previous report, the patient initiated dupilumab therapy after two unsuccessful prednisone tapers since his screening laboratory results were positive for *Mycobacterium tuberculosis* and hepatitis B core antibody. In the case presented here, our patient failed to fully respond to the standard treatment regimen, but achieved acceptable disease control with the addition of dupilumab. This case presents a likely clinical scenario in which biologics can be used in refractory cases and indicates that dupilumab may be effective when multiple other therapies have failed. Together, these two cases highlight a role for dupilumab in the treatment of pruritic disorders such as BP. Larger studies are

needed to ascertain the efficacy and dosing regimen for optimal therapeutic success.

Conclusion

In summary, dupilumab can ameliorate blistering and intractable pruritus in a patient with BP refractory to corticosteroids, multiple immunosuppressants, and omalizumab. Inhibiting the activity of Th2 cytokines, IL4 and IL13, by dupilumab is an intriguing therapeutic approach for BP, especially when pruritus cannot be controlled through conventional therapies.

Potential conflicts of interest

The authors declare no conflicts of interests.

Table 1. Comparison of key features in the currently reported case and a prior case report by Kaye et al. [30].

	Kaye et al. 2018, <i>JAMA Derm</i>	Current report
Age	80s	88-91
Sex	Male	Male
Clinical manifestations	Itching+blisters	Itching+blisters
Pathology	Eosinophil- and neutrophil-rich subepidermal bullae with 3+ linear IgG immunoreactivity along the DEJ	Spongiosis with focal epidermal and subepidermal vesicle formation and superficial dermal perivascular infiltrate containing eosinophils and lymphocytes, with linear IgG and C3 deposition at the DEJ
Serology	Undetectable BP180/BP230 after 3 months of therapy	Not measured
Prior treatments	Prednisone taper×2	Prednisone Clobetasol Triamcinolone acetonide Doxycycline Nicotinamide Mycophenolate mofetil Omalizumab Various antihistamines
Duration of prior treatments	Unspecified	2.5 years
Response to dupilumab	Itching improved within 1 week Blisters resolved within 1 month	Itching improved within 2 weeks Blisters resolved within 7 weeks

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