Seidman JS, Eichenfield DZ, Orme CM. Targeting Type 2 Inflammation for Treatment of Bullous Pemphigoid. J Dermatol & Skin Sci. 2020;2(1):29-33

Journal of Dermatology and Skin Science

Mini Review Article Open Access

Targeting Type 2 Inflammation for Treatment of Bullous Pemphigoid

Jason S Seidman[1], Dawn Z Eichenfield[2], Charisse M Orme[2]*

[1]School of Medicine, University of California San Diego, San Diego, California, USA
[2]Department of Dermatology, University of California San Diego, San Diego, California, USA

Article Info

Article Notes
Received: April 23, 2020
Accepted: April 28, 2020

***Correspondence:**
*Dr. Charisse M. Orme, 8899 University Center Lane, Suite 350, San Diego, California 92122, Tel: 858-657-8322, Email: chorme@ucsd.edu.

Keywords:
Dupilumab
Bullous pemphigoid
Pruritus
TH2 Cytokines
Type 2 Inflammation
IL-4
IL-13
IL-4Rα

Abstract

Bullous pemphigoid (BP) is an autoimmune blistering condition, often presenting in elderly individuals with pruritis and tense bullae. While standard treatment involves steroids, steroid sparing agents, and anti-inflammatory therapies, clinicians are increasingly utilizing novel biologics off-label for refractory cases. We recently reported a case of successful treatment of BP using dupilumab, a monoclonal interleukin 4 receptor alpha (IL-4Rα) antibody that modulates type 2 inflammation through dual inhibition of IL-4 and IL-13 signaling. Here, we discuss how the reported efficacy of dupilumab and certain other biologics in treating BP implicates type 2 inflammation as an important driver of BP pathogenesis. Furthermore, reports of dupilumab successfully treating patients with other pruritic dermatologic diseases highlight the importance of type 2 inflammation, particularly through IL-4R signaling, in chronic pruritis. The rapid development of these biologic therapies presents new opportunities for research and treatment of inflammatory dermatologic disorders.

Introduction

Bullous pemphigoid (BP) is an autoimmune blistering disease that commonly presents in elderly adults with clinical features of tense bullae and pruritis. Subepidermal blister formation in BP involves auto-antibodies directed against hemidesmosome proteins BP180 and/or BP230, leading to complement activation, mast cell degranulation, neutrophilic and eosinophil infiltration, and proteolysis at the dermal epidermal junction[1,2]. First-line treatments for BP include topical and oral corticosteroids, with steroid sparing immunosuppressive and anti-inflammatory agents utilized for long term management[3]. Treatment of refractory cases often involves off-label use of biologic agents such as rituximab[4-6] and omalizumab[6-8]. We recently reported a case of an elderly man with BP and intractable pruritis, who after failing conventional treatments and a trial of omalizumab, achieved satisfactory disease control with dupilumab[9].

Dupilumab is a human monoclonal IL-4Rα antibody approved for treatment of atopic dermatitis (AD), asthma, and chronic sinusitis with nasal polyposis, which modulates type 2 inflammation through inhibition of IL-4 and IL-13 signaling[10]. Here, we discuss how recent reports of biologics targeting type 2 inflammation suggest that this pathway may be an important driver of BP pathogenesis. Additionally, numerous reports of the efficacy of dupilumab in other chronic pruritic diseases indicate that it may be an especially useful anti-pruritic agent. The increasing development and usage of biologic therapies that potently and specifically inhibit disease relevant pathways represents an emerging paradigm in the study and treatment of autoimmune and inflammatory diseases.

Type 2 Inflammation in Bullous Pemphigoid

Type 2 inflammation involves a complex milieu of leukocytes and secreted proteins, which orchestrate defense against a wide range of environmental insults, including helminths, xenobiotics, and irritants[11]. The principal effectors include TH2 CD4+ T cells and group 2 innate lymphoid cells that produce type 2 cytokines IL-4, IL-5, and IL-13, B cells that secrete IgE, and granulocytes such as eosinophils, mast cells, and basophils. The actions of this pathway enable the body to remove offenders by eliciting physiologic responses such as mucous production and itch. Overactivity of type 2 inflammation is vital to the development of atopic disease such as allergy, asthma, and AD[12].

Several lines of evidence point to a prominent type 2 inflammatory response in BP, which include important roles of TH2 cytokines and chemokines, eosinophils, and IgE. Increased expression of IL-4 and IL-13[13,14] and amplified homing of IL-4 and IL-13 producing T cells[15] have been identified in BP skin lesions. Eosinophil chemoattractant IL-5 and eoxtaxins CCL11 and CCL26 are also found in high levels in BP blister fluid[16-18]. Eosinophils themselves are abundant in the lesions and peripheral blood of BP patients with recent studies suggesting that peripheral and lesional eosinophils are directly correlated with disease severity[19]. These observations have sparked interest in eosinophils as well as the cytokines and chemokines that regulate their biological functions in BP pathogenesis[20,21]. Intralesional eosinophils may amplify a local type 2 inflammatory response by releasing additional cytokines and chemokines[21], such as eotaxin and MCP-4, which function in a positive feedback loop and cause the recruitment of additional eosinophils[22]. Furthermore, eosinophils are an important source of the pruritogenic cytokine IL-31[23], and have also been proposed to promote itch in BP through pathways involving substance P, nerve growth factor, cross-talk with mast cells, and direct interactions with sensory and autonomic nerves[21].

While anti-BP180 and anti-BP230 IgG autoantibodies are well-established drivers of BP pathogenesis, IgE antibodies against these epitopes have also been shown to play an important role[1,2,7,19]. IgE production depends on IL-4 and IL-13 induced B cell class switching[12,24]. Elevated serum IgE is a hallmark of type 2 inflammation and is present in patients with BP[25], and increased IgE auto-antibodies targeting the NC16a domain of BP180 correlate with disease severity[26,27]. In mouse models, IgE auto-antibodies induce erythema, pruritis, blistering, and eosinophila[28,29]. Further studies have shown that eosinophils are necessary for anti-BP180 IgE-mediated skin blistering and participate in dermal epidermal junction (DEJ) separation through reactive oxygen species generation, release of eosinophilic granules, and eosinophil extracellular trap formation[21,30,31]. IgE-mediated DEJ splitting by eosinophils requires activation by the type 2 cytokine IL-5 and does not occur with anti-BP180 or anti-BP230 IgE autoantibodies alone[31].

Efficacy of Anti-Type 2 Inflammation Biologics in Bullous Pemphigoid

Multiple biologics that target the type 2 inflammatory axis have shown promise in the treatment of BP. Omalizumab, a humanized monoclonal antibody that binds IgE, was first reported to successfully treat refractory BP in 2009[7]. Subsequently, there have been multiple reports of successful off-label use in cases of refractory BP[6,8]. More recently, bertilumab, an anti-eoxtaxin-1 monoclonal antibody, showed positive results in an open, single arm phase II clinical trial and has been granted fast track designation for the treatment of BP[32]. The first case of successful treatment of BP with dupilumab was reported in 2018. This patient initiated dupilumab therapy after failing two prednisone tapers and positive screening results for *Mycobacterium tuberculosis* and hepatitis B core antibody, which limited his therapeutic options[33]. We reported a second case representative of a more typical clinical scenario warranting a trial of dupilumab - an elderly man who failed numerous conventional treatments and a trial of the more widely used omalizumab before initiating a trial of dupilumab[9]. Our patient experienced substantial reduction in itching after the first injection of dupilumab with resolution of blisters in the following weeks. Since our report, a case series has been published demonstrating clinical improvement in 12 out of 13 BP patients treated with dupilumab, with 7 patients achieving complete disease clearance[34]. A phase 2/3 clinical trial evaluating the efficacy and safety of dupilumab in BP is currently planned to start in June 2020 (NCT04206553).

Dupilumab has been approved for moderate to severe inadequately controlled AD, a more widely studied pruritic dermatologic condition involving type 2 inflammation[10,35]. In clinical trials, dupilumab has been effective in significantly reducing surface area involvement and severity of AD, as well as pruritis[10,35]. These studies showed a reduction of serum biomarkers for AD, including total IgE and CCL17. Skin lesions from AD patients treated with dupilumab showed reduced expression of TH2 cytokines and decreased activation of T cells, dendritic cells, and eosinophils, representative of a gene expression pattern more similar to normal skin than affected skin[10,35,36].

Patients treated with topical corticosteroids in combination with dupilumab showed a greater reduction in disease severity compared to corticosteroids plus placebo[10,35]. In these studies, patients treated dupilumab were also able to reduce their usage of topical corticosteroids and were less likely to require rescue therapy with other systemic medications[10]. Glucocorticoid

resistance is a phenomenon that frequently complicates treatment of inflammatory diseases such as asthma, rheumatoid arthritis, and inflammatory bowel disease, and has also been observed in AD[37]. IL-2, IL-4, and IL-13 evoke this phenomenon through a variety of mechanisms, which include altering alternative splicing of the glucocorticoid receptor (GR) to increase the inhibitory GRβ isoform, reducing the affinity of glucocorticoids for GR, reducing GR nuclear translocation, and increasing GR degradation through posttranslational modifications[37,38]. Since dupilumab inhibits IL-4 and IL-13, it, in turn, may increase the efficacy of glucocorticoid therapy by inhibiting IL-4 and IL-13 mediated glucocorticoid resistance.

Interestingly, omalizumab therapy, which also results in IgE reduction, did not offer improvement in moderate to severe AD and participants actually developed a slight worsening of itch compared to the control group[39]. We note that in our reported case, while the patient responded well to dupilumab, his symptoms failed to obtain regression with omalizumab treatment[9]. A potential advantage of dupilumab over omalizumab may be that blockade of IL-4Rα represents a more proximal point of inhibition in the type 2 inflammatory pathway[24]. IL-4 signaling is required for differentiation of TH2 CD4+ T cells and their production of type 2 cytokines including IL-5, IL-13, and eotaxins, isotype class switching to IgE in B cells, and recruitment of eosinophils[24]. Additionally, in atopic diseases, excessive IL-4Rα signaling impairs immune tolerance by subverting regulatory T cells into TH2-[40] and TH17-like T cells[41]. Thus, dupilumab may help maintain or re-establish immune tolerance by preventing excessive IL-4Rα mediated T cell subversion.

Efficacy of Dupilumab in Other Pruritic Dermatoses

Pruritus is a hallmark feature of BP, and can be the predominant symptom, with some patients never developing classic BP skin lesions[2,42]. In addition to AD and BP, dupilumab has shown promising results in other pruritic skin conditions, including chronic spontaneous urticaria[43], anal and genital itch[44], allergic contact dermatitis[45], prurigo nodularis[46-48], and other forms of chronic pruritis[49]. In addition to a phase 2/3 study in BP (NCT04206553), numerous clinical trials are now planned or currently underway to investigate dupilumab in the treatment of various pruritic skin diseases. These indications include hepatic pruritis (NCT04256759), cholinergic urticaria (NCT03749148), allergic contact dermatitis (NCT03935971), prurigo nodularis (NCT04183335 and NCT04202679), and chronic spontaneous urticaria (NCT03749135) with an additional trial in patients who failed omalizumab (NCT04180488).

Important itch mediators involved in type 2 inflammation include histamine, IL-4 and IL-13, IL-31, IL-33, TSLP and neuronal JAKs[50]. Recently, it has been shown that chronic itch is partly mediated by the actions of IL-4 and IL-13 on IL-4Rα expressed on sensory neurons[51]. This observation indicates that dupilumab may treat pruritus not only through decreasing type 2 inflammation, but also by directly inhibiting the neuronal sensory pathways that mediate itch.

Conclusion

The continued expansion of medical knowledge and development of novel targeted therapeutics has led to an increasing interest in personalizing therapeutic interventions based on disease pathogenesis, with genomics data and various biomarkers helping to inform these decisions. Case reports and other descriptive research into off-label usage of biologics provide useful information that helps guide treatment decisions for patients who have otherwise exhausted therapeutic options. Furthermore, these reports help to generate hypotheses about disease mechanisms that can be tested in basic scientific research and controlled clinical trials. This approach is especially intriguing in dermatology, where there is an expansive set of diseases that individually may have low prevalence but share common immunological mechanisms. For BP and other conditions where type 2 inflammation may play an important role, further studies can address whether biomarkers such as elevated serum IgE and eosinophilia can predict greater beneficial response to dupilumab and other therapies targeting this pathway.

Acknowledgements

DE is supported by research grants from the Women's Dermatologic Society and the Pediatric Dermatology Research Alliance.

Potential Conflicts of Interest

The authors declare no conflicts of interests.

References

1. Lo Schiavo A, Ruocco E, Brancaccio G, et al. Bullous pemphigoid: etiology, pathogenesis, and inducing factors: facts and controversies. Clin Dermatol. 2013; 31(4): 391-399.
2. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013; 381(9863): 320-332.
3. Bernard P, Antonicelli F. Bullous Pemphigoid: A Review of its Diagnosis, Associations and Treatment. Am J Clin Dermatol. 2017; 18(4): 513-528.
4. Lourari S, Herve C, Doffoel-Hantz V, et al. Bullous and mucous membrane pemphigoid show a mixed response to rituximab: experience in seven patients. J Eur Acad Dermatol Venereol. 2011; 25(10): 1238-1240.
5. Kasperkiewicz M, Shimanovich I, Ludwig RJ, et al. Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. J Am Acad Dermatol. 2011; 65(3): 552-558.
6. Kremer N, Snast I, Cohen ES, et al. Rituximab and Omalizumab for

the Treatment of Bullous Pemphigoid: A Systematic Review of the Literature. Am J Clin Dermatol. 2019; 20(2): 209-216.

7. Fairley JA, Baum CL, Brandt DS, et al. Pathogenicity of IgE in autoimmunity: successful treatment of bullous pemphigoid with omalizumab. J Allergy Clin Immunol. 2009; 123(3): 704-705.
8. Yu KK, Crew AB, Messingham KA, et al. Omalizumab therapy for bullous pemphigoid. J Am Acad Dermatol. 2014; 71(3): 468-474.
9. Seidman JS, Eichenfield DZ, Orme CM. Dupilumab for bullous pemphigoid with intractable pruritus. Dermatol Online J. 2019; 25(11).
10. Gooderham MJ, Hong HC, Eshtiaghi P, et al. Dupilumab: A review of its use in the treatment of atopic dermatitis. J Am Acad Dermatol. 2018; 78(3 Suppl 1): S28-S36.
11. Palm NW, Rosenstein RK, Medzhitov R. Allergic host defences. Nature. 2012; 484(7395): 465-472.
12. Kay AB. Allergy and allergic diseases. First of two parts. N Engl J Med. 2001; 344(1): 30-37.
13. Rico MJ, Benning C, Weingart ES, et al. Characterization of skin cytokines in bullous pemphigoid and pemphigus vulgaris. Br J Dermatol. 1999; 140(6): 1079-1086.
14. Schmidt E, Bastian B, Dummer R, et al. Detection of elevated levels of IL-4, IL-6, and IL-10 in blister fluid of bullous pemphigoid. Arch Dermatol Res. 1996; 288(7): 353-357.
15. Teraki Y, Hotta T, Shiohara T. Skin-homing interleukin-4 and -13-producing cells contribute to bullous pemphigoid: remission of disease is associated with increased frequency of interleukin-10-producing cells. J Invest Dermatol. 2001; 117(5): 1097-1102.
16. Ameglio F, D'Auria L, Bonifati C, et al. Cytokine pattern in blister fluid and serum of patients with bullous pemphigoid: relationships with disease intensity. Br J Dermatol. 1998; 138(4): 611-614.
17. Wakugawa M, Nakamura K, Hino H, et al. Elevated levels of eotaxin and interleukin-5 in blister fluid of bullous pemphigoid: correlation with tissue eosinophilia. Br J Dermatol. 2000; 143(1): 112-116.
18. Gunther C, Wozel G, Meurer M, et al. Up-regulation of CCL11 and CCL26 is associated with activated eosinophils in bullous pemphigoid. Clin Exp Immunol. 2011; 166(2): 145-153.
19. Messingham KN, Crowe TP, Fairley JA. The Intersection of IgE Autoantibodies and Eosinophilia in the Pathogenesis of Bullous Pemphigoid. Front Immunol. 2019; 10: 2331.
20. Simon D, Borradori L, Simon HU. Eosinophils as putative therapeutic targets in bullous pemphigoid. Exp Dermatol. 2017; 26(12): 1187-1192.
21. Amber KT, Valdebran M, Kridin K, et al. The Role of Eosinophils in Bullous Pemphigoid: A Developing Model of Eosinophil Pathogenicity in Mucocutaneous Disease. Front Med (Lausanne). 2018; 5: 201.
22. Gounni Abdelilah S, Wellemans V, Agouli M, et al. Increased expression of Th2-associated chemokines in bullous pemphigoid disease. Role of eosinophils in the production and release of these chemokines. Clin Immunol. 2006; 120(2): 220-231.
23. Rudrich U, Gehring M, Papakonstantinou E, et al. Eosinophils are a Major Source of Interleukin-31 in Bullous Pemphigoid. Acta Derm Venereol. 2018; 98(8): 766-771.
24. Gandhi NA, Bennett BL, Graham NM, et al. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov. 2016; 15(1): 35-50.
25. Soh H, Hosokawa H, Asada Y. IgE and its related phenomena in bullous pemphigoid. Br J Dermatol. 1993; 128(4): 371-377.
26. Kalowska M, Ciepiela O, Kowalewski C, et al. Enzyme-linked Immunoassay Index for Anti-NC16a IgG and IgE Auto-antibodies Correlates with Severity and Activity of Bullous Pemphigoid. Acta Derm Venereol. 2016; 96(2): 191-196.
27. Ishiura N, Fujimoto M, Watanabe R, et al. Serum levels of IgE anti-BP180 and anti-BP230 autoantibodies in patients with bullous pemphigoid. J Dermatol Sci. 2008; 49(2): 153-161.
28. Fairley JA, Burnett CT, Fu CL, et al. A pathogenic role for IgE in autoimmunity: bullous pemphigoid IgE reproduces the early phase of lesion development in human skin grafted to nu/nu mice. J Invest Dermatol. 2007; 127(11): 2605-2611.
29. Zone JJ, Taylor T, Hull C, et al. IgE basement membrane zone antibodies induce eosinophil infiltration and histological blisters in engrafted human skin on SCID mice. J Invest Dermatol. 2007; 127(5): 1167-1174.
30. Lin L, Hwang BJ, Culton DA, et al. Eosinophils Mediate Tissue Injury in the Autoimmune Skin Disease Bullous Pemphigoid. J Invest Dermatol. 2018; 138(5): 1032-1043.
31. de Graauw E, Sitaru C, Horn M, et al. Evidence for a role of eosinophils in blister formation in bullous pemphigoid. Allergy. 2017; 72(7): 1105-1113.
32. Izumi K, Bieber K, Ludwig RJ. Current Clinical Trials in Pemphigus and Pemphigoid. Front Immunol. 2019; 10: 978.
33. Kaye A, Gordon SC, Deverapalli SC, et al. Dupilumab for the Treatment of Recalcitrant Bullous Pemphigoid. JAMA Dermatol. 2018; 154(10): 1225-1226.
34. Abdat R, Waldman RA, de Bedout V, et al. Dupilumab as a Novel Therapy for Bullous Pemphigoid: A Multicenter Case Series. J Am Acad Dermatol. 2020.
35. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014; 371(2): 130-139.
36. Hamilton JD, Suarez-Farinas M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2014; 134(6): 1293-1300.
37. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet. 2009; 373(9678): 1905-1917.
38. Dejager L, Vandevyver S, Petta I, et al. Dominance of the strongest: inflammatory cytokines versus glucocorticoids. Cytokine Growth Factor Rev. 2014; 25(1): 21-33.
39. Heil PM, Maurer D, Klein B, et al. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course - a randomized, placebo-controlled and double blind pilot study. J Dtsch Dermatol Ges. 2010; 8(12): 990-998.
40. Noval Rivas M, Burton OT, Wise P, et al. Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy. Immunity. 2015; 42(3): 512-523.
41. Massoud AH, Charbonnier LM, Lopez D, et al. An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to TH17-like cells. Nat Med. 2016; 22(9): 1013-1022.
42. Bakker CV, Terra JB, Pas HH, et al. Bullous pemphigoid as pruritus in the elderly: a common presentation. JAMA Dermatol. 2013; 149(8): 950-953.
43. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. J Allergy Clin Immunol Pract. 2019; 7(5): 1659-1661 e1651.
44. Yang EJ, Murase JE. Recalcitrant anal and genital pruritus treated with dupilumab. Int J Womens Dermatol. 2018; 4(4): 223-226.
45. Machler BC, Sung CT, Darwin E, et al. Dupilumab use in allergic contact dermatitis. J Am Acad Dermatol. 2019; 80(1): 280-281 e281.

46. Beck KM, Yang EJ, Sekhon S, et al. Dupilumab Treatment for Generalized Prurigo Nodularis. JAMA Dermatol. 2019; 155(1): 118-120.

47. Mollanazar NK, Elgash M, Weaver L, et al. Reduced Itch Associated With Dupilumab Treatment In 4 Patients With Prurigo Nodularis. JAMA Dermatol. 2018.

48. Napolitano M, Fabbrocini G, Scalvenzi M, et al. Effectiveness of Dupilumab for the Treatment of Generalized Prurigo Nodularis Phenotype of Adult Atopic Dermatitis. Dermatitis. 2020.

49. Zhai LL, Savage KT, Qiu CC, et al. Chronic Pruritus Responding to Dupilumab-A Case Series. Medicines (Basel). 2019; 6(3).

50. Trier AM, Kim BS. Cytokine modulation of atopic itch. Curr Opin Immunol. 2018; 54: 7-12.

51. Oetjen LK, Mack MR, Feng J, et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. Cell. 2017; 171(1): 217-228 e213.