Targeting Type 2 Inflammation for Treatment of Bullous Pemphigoid

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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 junction¹,². First-line treatments for BP include topical and oral corticosteroids, with steroid sparing immunosuppressive and anti-inflammatory agents utilized for long term management³. Treatment of refractory cases often involves off-label use of biologic agents such as rituximab⁴,⁵ and omalizumab⁶,⁸. 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 dupilumab⁹.

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 signaling¹⁰. 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. 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 mucus production and itch. Overactivity of type 2 inflammation is vital to the development of atopic disease such as allergy, asthma, and AD.

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 and amplified homing of IL-4 and IL-13 producing T cells have been identified in BP skin lesions. Eosinophil chemoattractant IL-5 and eotaxins CCL11 and CCL26 are also found in high levels in BP blister fluid. 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. These observations have sparked interest in eosinophils as well as the cytokines and chemokines that regulate their biological functions in BP pathogenesis. Intralesional eosinophils may amplify a local type 2 inflammatory response by releasing additional cytokines and chemokines, such as eotaxin and MCP-4, which function in a positive feedback loop and cause the recruitment of additional eosinophils. Furthermore, eosinophils are an important source of the pruritogenic cytokine IL-31, 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.

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. IgE production depends on IL-4 and IL-13 induced B cell class switching. Elevated serum IgE is a hallmark of type 2 inflammation and is present in patients with BP, and increased IgE auto-antibodies targeting the NC16a domain of BP180 correlate with disease severity. In mouse models, IgE auto-antibodies induce erythema, pruritis, blistering, and eosinophilia. 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.

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.

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. Subsequently, there have been multiple reports of successful off-label use in cases of refractory BP. More recently, belimumab, an anti-eotaxin-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.

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. 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. 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. 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. In clinical trials, dupilumab has been effective in significantly reducing surface area involvement and severity of AD, as well as pruritus. 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. Patients treated with topical corticosteroids in combination with dupilumab showed a greater reduction in disease severity compared to corticosteroids plus placebo. In these studies, patients treated with dupilumab were also able to reduce their usage of topical corticosteroids and were less likely to require rescue therapy with other systemic medications. 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. 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. 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. We note that in our reported case, while the patient responded well to dupilumab, his symptoms failed to obtain regression with omalizumab treatment. 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. 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 eosinophils, IL-4Rα signaling impairs immune tolerance by subverting regulatory T cells into TH2 and TH17-like T cells. 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. In addition to AD and BP, dupilumab has shown promising results in other pruritic skin conditions, including chronic spontaneous urticaria, anal and genital itch, allergic contact dermatitis, and recruitment of eosinophils. Additionally, in atopic diseases, excessive IL-4Rα signaling impairs immune tolerance by subverting regulatory T cells into TH2 and TH17-like T cells. Thus, dupilumab may help maintain or re-establish immune tolerance by preventing excessive IL-4Rα mediated T cell subversion.

Inflammation include histamine, IL-4 and IL-13, IL-31, IL-33, TSLP and neuronal JAKs. 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. 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.

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Potential Conflicts of Interest

The authors declare no conflicts of interests.

References


