Dupilumab for Bullous Pemphigoid: To Treat or Not to Treat?

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PRACTICE **POINTS**

- Bullous pemphigoid (BP) is a pruritic autoimmune blistering disease in older adults that often requires systemic therapy with associated risks.
- Dupilumab targets interleukin (IL) 4/IL-13–driven inflammation and shows promising efficacy in BP.
- As the first approved biologic for BP, dupilumab may offer a safer alternative to corticosteroids in select patients.

Bullous pemphigoid (BP) is a chronic autoimmune skin condition characterized by large, fluid-filled blisters (bullae) on the skin. There usually is severe itching, which may antedate the bullae by several weeks. Bullous pemphigoid most commonly affects adults aged 60 years and older with comorbidities such as metabolic syndrome or other autoimmune diseases. The typical blistering is subepidermal, and its occurrence seems to be driven by autoantibodies targeting the epidermal basement membrane zone.

Conventional treatment for BP has long included systemic corticosteroids and immunosuppressants; this combination of drugs effectively controls inflammation but also is associated with considerable risks such as infection, hyperglycemia with worsening diabetes, hypertension, osteoporosis and fracture risk, and delirium, particularly in older patients. Recent developments in biologic therapy have supported the utilization of potentially safer alternatives. Specifically, dupilumab has demonstrated efficacy in the treatment of atopic dermatitis. Case reports and small research studies included in a recent review have suggested that dupilumab could be effective in managing BP, potentially offering a safer treatment option.[1] Importantly, dupilumab recently was approved for BP by the US Food and Drug Administration, making it the first biologic approved for treating this condition.[2] In this article, we discuss dupilumab as an option for clinicians to prescribe as an initial therapy for BP.

Pathophysiology of Bullous Pemphigoid and Dupilumab

Bullous pemphigoid pathophysiology is driven by 2 main components: immunologic and inflammatory processes. The immune-mediated attack consists of autoantibodies against the hemidesmosomal proteins BP180 and BP230 in the basement membrane zone, which anchor the epidermis to the dermis.[1] When these proteins are targeted, a cascade of responses is triggered, including the release of inflammatory cells, particularly eosinophils and neutrophils, into the skin. These cells release inflammatory mediators that break down the basement membrane, resulting in the separation of the epidermis from the dermis and leading to subepidermal blister formation.

The inflammation associated with BP largely is driven by a T helper 2–dominant immune response, with increased levels of cytokines such as interleukin (IL) 4 and IL-13.[1] The chronic inflammation contributes to the characteristic blisters and intense pruritus seen in patients with BP. Traditional treatments such as corticosteroids work broadly to suppress this inflammation by reducing the production of all proinflammatory cytokines; however, they lack specificity, which dampens the targeted immune response against BP and broadly suppresses the immune system, increasing the risk for infection and other adverse effects. For older patients with multiple health conditions, these adverse effects can impact quality of life and pose health risks.

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Interleukin 4 and IL-13 contribute to eosinophilia by upregulating the expression of eosinophil chemoattractant cytokines that promote eosinophil migration and adhesion.[1] This is where dupilumab presents a promising alternative. Dupilumab is a monoclonal antibody that selectively targets the key cytokines implicated in BP. It binds to the IL-4 receptor alpha subunit, which IL-4 and IL-13 share, thereby inhibiting the signaling of both cytokines.[1]

Dupilumab Reports and Case Series

Current evidence supporting the use of dupilumab for BP consists primarily of case series and uncontrolled clinical observations, both of which are useful to formulate but not to test hypotheses.[3] One case series of 13 patients diagnosed with BP reported that 92.3% (12/13) of patients achieved disease clearance or satisfactory control, with 53.8% (7/13) achieving total lesion clearance and no adverse events observed.[4] In a larger case series, 87.0% of 146 patients achieved disease control with an initial dose of dupilumab 600 mg followed by 300 mg every 2 weeks for 4 weeks, though the study also looked at secondary outcomes for up to 64 weeks.[5] Both these findings are compatible with the idea that dupilumab has efficacy in BP, but they cannot be used to test hypotheses.[3,4]

In a single case report of refractory BP, the combination of dupilumab and omalizumab—a monoclonal antibody that blocks the binding of IgE to mast cells, basophils, and dendritic cells—has shown efficacy, particularly when BP is unresponsive to standard therapies.[6] The case involved a 72-year-old woman with unresponsive BP who was treated with a combination of dupilumab and omalizumab. She experienced marked improvement in pruritus and bullae accompanied by normalization of anti-BP180 autoantibody levels. This result points to the possibility that IL-4 and IL-13 blockade could influence autoantibody production. The authors attributed the reduction in pruritus to dupilumab, although the drug was administered in combination with omalizumab.[6]

Small Randomized Trial of Dupilumab

In addition to these uncontrolled clinical observations, dupilumab recently demonstrated positive results in a small randomized trial.[7] Patients who were assigned to receive dupilumab were 5 times more likely to achieve sustained remission compared to those assigned to a placebo. All randomized patients also were treated with a standard-of-care oral corticosteroid regimen, which complicated the ability to isolate the specific effects of dupilumab.[7] Finally, a completed totality of evidence on the prescription of dupilumab for refractory BP should include more reliable results from larger randomized trials.[8]

Final Thoughts

Dupilumab is now approved by the US Food and Drug Administration for the treatment of BP, marking an important milestone as the first targeted biologic therapy for this condition. While the totality of evidence is still evolving, the available data indicate both efficacy and a favorable safety profile when compared to traditional corticosteroids and immunosuppressants. Based on the available data, we suggest that health care providers consider dupilumab as a first-line monotherapy in appropriate patients with BP without specific contraindications, particularly as a practical and safe alternative to corticosteroids and immunosuppressive therapies in older adults with comorbidities. If the patient demonstrates clinical improvement in symptom relief, the therapy can be continued. This strategy minimizes initial exposure to more potent biologics or therapies with higher toxicity profiles. For patients without adequate disease control or with severe initial presentations requiring rapid improvement, clinicians may consider escalation to adjunctive or alternative therapies, such as rituximab, omalizumab, or a short course of systemic corticosteroids for acute management.

Emerging data suggest that dupilumab is a promising therapy for BP. We suggest that it may be a safer targeted alternative to traditional corticosteroids and immunosuppressive therapies. The ability of dupilumab to mitigate inflammation without broadly suppressing the immune system suggests that it may turn out to be an especially valuable option for older patients and those with comorbid conditions.

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