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Reviewing the current treatment approaches for bullous pemphigoid – analysis of literature

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Abstract

Introduction:

Bullous pemphigoid (BP) is an autoimmune blistering disorder primarily affecting the elderly, particularly older men, and is characterized by type 2 inflammation. The disease is defined by autoantibodies targeting BP180 (BPAG2) and BP230 (BPAG1) within the basement membrane zone. Advanced age is a significant risk factor for BP, with additional associations identified, including certain medications—such as dipeptidyl peptidase-4 inhibitors and aldosterone antagonists—and neurological disorders like Parkinson's disease.

The global annual cumulative incidence of BP is estimated at 8.2 cases per 1,000,000 individuals, with Europe reporting higher incidence rates than other regions. BP significantly impacts patients' quality of life due to painful, pruritic skin lesions and is associated with a higher prevalence of psychiatric comorbidities, such as schizophrenia.

BP increases the risk of complications, including pulmonary embolism and pneumonia, and is linked to high mortality. These findings highlight the need for early diagnosis and comprehensive management to improve patient outcomes.

Aim of the study:

The purpose of the study is to summarize the available knowledge about options for bullous pemphigoid treatment. The options in treatment, including the latest methods, were described and summarized.

Materials and methods:

Literature available in the PubMed database was reviewed using the following keywords:

"Bullous pemphigoid", "Pemphigoid", "Bullous pemphigoid Treatment", "New Bullous pemphigoid Treatment", "Systemic Therapy for bullous pemphigoid"

Conclusions:

Bullous pemphigoid is an autoimmune blistering disease with complex pathogenesis involving IgG and IgE autoantibodies, complement activation, and type 2 inflammation. Treatment balances efficacy and safety, especially for elderly patients. High-potency topical corticosteroids are the first-line therapy, with systemic corticosteroids and immunosuppressants used for severe cases. Biologics like dupilumab, rituximab, and omalizumab show promise in refractory cases, with omalizumab offering high efficacy and minimal side effects. Experimental therapies, including complement modulators and targeted anti-inflammatory agents like reslizumab and diacerein, are under study. Innovative approaches, such as low-dose IL-2 therapy and JAK inhibitors, highlight advancements in disease control. Personalized strategies aim to improve outcomes, reduce steroid use, and enhance safety.

Key words: Bullous pemphigoid; autoimmune blistering disease; corticosteroids therapy

Introduction

Bullous pemphigoid (BP) is an autoimmune blistering disorder characterized by features of type 2 inflammation, typically affecting the elderly population, particularly older men. [1,2] It is defined by the presence of autoantibodies targeting two proteins within the basement membrane zone: BP180 (BPAG2) and BP230 (BPAG1). The etiology of bullous pemphigoid remains incompletely understood; however, advanced age is widely acknowledged as the primary factor contributing to its development. Emerging evidence increasingly implicates certain medications, such as dipeptidyl peptidase-4 inhibitors, aldosterone antagonists, anticholinergics, and dopaminergic medications, in its pathogenesis [3,4]. Neurological disorders, including Parkinson's disease, have also been associated with the development of BP. [5,6]

Globally, the pooled annual cumulative incidence of bullous pemphigoid is estimated to

be 8.2 cases per 1,000,000 individuals. Notably, most studies were conducted exclusively in Europe and Asia, with Europe demonstrating a higher incidence. Increased incidence rates were observed in adult populations, population-based studies, and during more recent study periods. Additionally, the pooled incidence rate of bullous pemphigoid was calculated to be 34.2 cases per 1,000,000 person-years.[7]

Skin lesions in bullous pemphigoid, along with associated symptoms such as pain and itching, can severely affect the quality of life of patients. **P**atients with BP exhibited a significantly higher prevalence of psychiatric disorders, especially schizophrenia. [8,9]

The risk of developing pulmonary embolism or pneumonia was found to be increased following a diagnosis of BP, and BP itself is associated with high mortality. The prognostic factors for mortality in bullous pemphigoid are positive bullous pemphigoid 180 antibody, dementia, stroke, heart disease and diabetes mellitus. [10,11]

Pathogenesis

The pathogenesis of bullous pemphigoid involves both complement-dependent and complement-independent mechanisms. BP is primarily characterized by IgG autoantibodies targeting BP180 and BP230, which are components of hemidesmosomes involved in dermal-epidermal cohesion. Almost all BP patients have circulating IgG autoantibodies against BP180, particularly the BP180-NC16A domain, which plays a significant role in BP pathogenesis. IgG4 is the dominant subclass in BP, although its exact role remains unclear.[1].

Several studies have identified IgE autoantibodies against BP230, with some linking IgE anti-BP230 reactivity to eosinophil accumulation. IgE anti-BP230 levels often correlate with total serum IgE levels. In contrast, IgE anti-BP180 autoantibodies are strongly associated with disease activity and can induce cytokine release and BP180 internalization in keratinocytes. [12] Inflammatory cell infiltration, including mast cells, neutrophils, and eosinophils, is common in BP lesions. Mast cell degranulation leads to the release of inflammatory cytokines and proteases, contributing to skin barrier damage. Neutrophils play a significant role, as blocking their infiltration prevents blistering, while IL-8 induces blistering. Eosinophils amplify type 2 inflammation in BP lesions and participate in blister formation through cytokine release and toxic protein production.

Type 2 inflammatory cytokines (IL-4, IL-5, IL-13) and chemokines (eotaxins, MCP-4, TARC) are elevated in BP lesions, with IL-4 and IL-13 driving type 2 inflammation. These cytokines may contribute to eosinophilia and mast cell activation, with IL-4 enhancing IgE

crosslinking and potentiating inflammatory gene expression in mast cells. Additionally, IL-4 and IL-13 influence pruritus by sensitizing sensory neurons. [1,13,14]

A recent meta-analysis indicates a significant association between bullous pemphigoid and the use of diuretics, particularly aldosterone antagonists, dipeptidyl peptidase-4 inhibitors, anticholinergics, and dopaminergic medications. Other drugs whose roles remain uncertain have occasionally been reported to be associated with the onset of BP, such as NSAIDs, antibiotics, ACE inhibitors, and TNF-alpha inhibitors. [15]

A meta-analysis by Dhaouadi T demonstrated a significant association between the DRB11101, DQA10505, and DQB10301 alleles and increased pemphigoid risk. Compared to idiopathic pemphigoid, these associations were notably stronger in drug-induced pemphigoid. In contrast, the DQA10201 allele appears to exert a protective effect against pemphigoid. [16]

Diagnosis

The diagnosis of bullous pemphigoid should be established based on specific criteria. In most cases, the diagnosis relies on the presence of suggestive clinical features, particularly when at least three of the following four characteristics are observed: the patient is older than 70 years, there are no atrophic scars, there is no mucosal involvement, and predominant bullous lesions are absent on the neck and head. [2,15]

For patients presenting with non-bullous lesions, the diagnosis of BP can be made if DIF studies are positive and circulating IgG autoantibodies are detected. These autoantibodies must bind to the epidermal side of split skin (SSS) by Indirect Immunofluorescence (IIF) microscopy or react with BP180 and/or BP230 through ELISA or IIF. [12]

If DIF studies are negative, it is recommended to perform a repeat biopsy to rule out technical issues. In cases where negative DIF findings persist, the diagnosis of BP can still be accepted if the clinical presentation is suggestive, characterized by the presence of tense blisters. Furthermore, histopathological findings should confirm subepidermal cleavage, and circulating IgG autoantibodies must be detected binding to the epidermal side of SSS by IIF microscopy. Additionally, serum reactivity with BP180 and/or BP230 must be demonstrated using ELISA or IIF. [2,15]

Treatment

Treatment for BP depends on its severity and the patient's comorbidities. High-potency topical corticosteroids are the preferred option, while oral prednisone (0.5 mg/kg/day) is a recommended alternative. If corticosteroids are contraindicated or ineffective, immunosuppressants like methotrexate, azathioprine, or mycophenolate may be used. The roles of doxycycline and dapsone remain debated but may be suitable for patients unable to take corticosteroids. For resistant cases, B-cell-depleting therapy or intravenous immunoglobulins can be considered. Emerging treatments, including omalizumab and dupilumab, show promise. [15]

Meta-analysis indicated that anti-BP180 autoantibody levels may serve as an adjunctive tool for monitoring BP disease severity and guiding clinical care for patients with BP. [17]
The primary treatment options include oral and/or topical high-potency corticosteroids, often used in combination with immunomodulatory agents like dapsone and tetracyclines, or immunosuppressive drugs such as azathioprine and methotrexate.
Recent case reports describing the effective use of the anti-IgE antibody omalizumab in treating individual BP patients highlight the potential pathogenic role of IgE autoantibodies in the disease. [12]

Systemic glucocorticoids

Systemic corticosteroids remain the treatment with the strongest evidence for efficacy in bullous pemphigoid. National guidelines highlight that the primary goal of treating pemphigoid diseases is to block the pathological signaling caused by autoantibodies. Systemic prednisolone is typically started at doses below 0.5–0.6 mg/kg/day, as higher doses (>0.75 mg/kg/day) increase the risk of side effects and mortality without added benefit. Maintenance therapy involves tapering glucocorticoids to the lowest effective dose, with treatment usually lasting 9–12 months. [4]

However, their use is associated with significant risks, including the development of diabetes, infections, osteoporosis, and hypertension. [18]

High potency topical corticosteroids

Very potent topical corticosteroids (e.g., clobetasol propionate) have proven effective in BP, with lower morbidity and mortality compared to oral prednisone at 1 mg/kg/day, but they present challenges in application and notable cutaneous toxicity. Studies have shown that potent topical corticosteroids are an effective option for moderate to severe BP and are superior to oral prednisone (1 mg/kg daily) in patients with extensive disease, particularly in terms of side effects and overall survival.[19]

As a result, several national guidelines now recommend topical steroid therapy as the first-line treatment for BP.It should be applied once or twice daily over the entire body, covering both healthy skin and affected areas (excluding the face) until disease control is achieved. Disease control is defined as the absence of new lesions or itching, with existing lesions showing signs of healing.[18]

After achieving control, the same dosage of the cream is maintained for 15 days, followed by a gradual tapering over 4 to 12 months.[20] Clobetasol propionate is highly effective, but it can be difficult to use in the home setting, particularly for elderly patients.[19] A drawback is the practical and economic challenges associated with prolonged nursing care and/or the cost of long-term use of high-potency topical corticosteroids. [15]

Doxycycline

Doxycycline, a derivative of first-generation tetracyclines, is an antibiotic with broad-spectrum bacteriostatic properties. It inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit, targeting both gram-positive and gram-negative bacteria. Moreover, doxycycline can also interact with the 40S ribosomal subunit, specific to mammalian cells, indicating reduced target specificity. [21]

Certain characteristics, such as cytokine regulation, antioxidant activity, inhibition of protease-activated receptor 2 (PAR2), suppression of matrix metalloproteinases (MMPs), prevention of collagen degradation, and inhibition of leukocyte chemotaxis, are believed to contribute to its anti-inflammatory effects. [22]

The study showed that starting bullous pemphigoid treatment with 200 mg of doxycycline daily provides acceptable short-term effectiveness within the predefined non-inferiority margin, along with significant safety improvements at 1 year compared to

prednisolone 0.5 mg/kg per day. No clear evidence was found that differences between the two treatment strategies varied by baseline disease severity, suggesting that both strategies have modest effectiveness in severe cases. [23]

Steroid sparing agents

Azathioprine

Azathioprine is a pro-drug that is swiftly transformed into 6-mercaptopurine (6-MP) through the purine metabolism pathway. Its therapeutic effects arise from its action as a purine anti-metabolite. As a purine analogue, it interferes with DNA synthesis and affects cells with high proliferation rates.[24]

Starting a steroid-sparing agent since the initiation of treatment is advisable. Time of onset of the therapeutic effects for azathioprine varies from one week to seven months. At a four-year follow-up, 44% of patients achieve remission of the disease.It halts disease progression and promotes re-epithelialization as soon as eight weeks of starting treatment. [25] Mycophenolate mofetil and azathioprine show comparable effectiveness in treating bullous pemphigoid, with both groups receiving similar cumulative doses of corticosteroids to manage the condition.[26]

Methotrexate

Methotrexate primarily interacts with physiological processes such as the folate pathway, adenosine signaling, and the regulation of prostaglandins, leukotrienes, and cytokines. Its polyglutamation modifies pharmacokinetics and pharmacodynamics, enhancing and extending its therapeutic effects.[27]

An initial MTX dose above 7.5 mg, ideally 10 mg, is recommended to achieve remission without further increases. In this study, 25% of patients required dose adjustments due to insufficient remission, with over half starting at 7.5 mg/week. Adding steroids should not depend on the time to remission. Studies indicate that increasing MTX doses to achieve therapeutic effects typically reaches 12.5–17.5 mg/week, with disease severity affecting remission time. Due to relapses during dose reductions or rapid withdrawal, 85% of patients remained on a minimal MTX dose (mean: 4.88 ± 2.32 mg/week) for several months. MTX monotherapy is preferred in elderly BP patients to avoid steroid-related side effects. [28,29]

The retrospective study evaluated the efficacy and tolerability of a combination therapy of methylprednisolone and low-dose methotrexate (up to 12.5 mg/week) for BP. After 12 weeks, 96.4% of patients treated over a five-year period remained on therapy. BP remission was achieved in all adherent cases, including 24 associated with dipeptidyl peptidase-4 inhibitors with a mean cumulative MP dose of 678.4 ± 49.4 mg. At three years, 73.4% of patients remained free of relapses. [30]

Mycophenolate mofetil

Mycophenolate mofetil (MMF), an inhibitor of inosine monophosphate dehydrogenase with notable anti-inflammatory effects, could serve as a potential alternative to systemic glucocorticoids in the management of BP. MMF therapy began at 500–1000 mg BID, gradually increasing monthly by 500 mg BID to a maximum of 3000 mg BID. Administered alone or with prednisone, it improved all patients within 0.8 months on average, achieving complete disease control in 96.2% of cases within 5.6 months. Sustained remission for up to 15 months post-discontinuation occurred in 46.2% of patients, more often with combination therapy (57.1%) than monotherapy (33.3%). Mild adverse effects were reported in 12 cases, with one discontinuation due to gastrointestinal symptoms. MMF is a safe, effective treatment for BP, achieving significant improvement and remission in many patients.[31]

Mycophenolate mofetil and azathioprine are equally effective in treating bullous pemphigoid, with both requiring comparable cumulative corticosteroid doses for disease control. However, mycophenolate mofetil is associated with significantly lower liver toxicity compared to azathioprine. [32]

Dapsone

Dapsone or 4,4'-diaminodiphenylsulfone is a chemotherapeutic agent that belongs to the sulfonamide class of antibiotics. Dapsone's anti-inflammatory effects have been attributed to its ability to inhibit neutrophil migration and reduce the production of toxic secretory substances that harm the skin. [33]

Dapsone effectively alleviates disease in the antibody transfer model of BP-like EBA in a dose-dependent manner. A dose of 10.0 mg/kg significantly improved BP-like EBA, though less effectively than the 100 mg/kg dose. Dapsone notably reduced inflammation in BP model by decreasing neutrophil recruitment to the skin and inhibiting the release of leukotriene B4 (LTB4) and reactive oxygen species (ROS) in response to immune complexes. LTB4 is involved

in various diseases, but no effective inhibitors are available for clinical use. These findings suggest that dapsone's action in these models may involve the suppression of LTB4 and ROS release from neutrophils. [34]

Cyclosporin

Cyclosporine A suppresses T cell responses by blocking IL-2 production. In dendritic cells, crucial for T cell priming, it modulates surface molecule expression and cytokine secretion, altering T cell activation. In macrophages and neutrophils, key players in antimicrobial defense, it reduces cytokine production. Additionally, Cyclosporine A inhibits the release of mitochondrial factors that drive type 1 interferon production by innate immune cells.[35]

Cyclosporine serves as an alternative treatment for managing bullous pemphigoid coexisting with psoriasis. This condition poses a significant challenge, as many physical treatments and topical agents effective for psoriasis can trigger bullous lesions. Additionally, systemic steroids, commonly used to treat bullous pemphigoid, may exacerbate psoriasis or lead to pustular psoriasis flare-ups after their discontinuation.[36]

In the study by Thivolet et al., Patient 1 with bullous pemphigoid began treatment with very low doses of prednisone. After one month, more blistering lesions appeared, and cyclosporine was introduced. The lesions healed 20 days later. Two months after starting cyclosporine, prednisone was discontinued. One month later, both clinical and immunological remission remained stable.

Patient 2, diagnosed with bullous pemphigus, was treated with cyclosporine alone. Clinical remission was achieved within one month, and treatment was discontinued. Two months later, the patient remained disease-free. The cyclosporine treatment lasted three months. No adverse effects from cyclosporine were observed in these patients. [37]

Intravenous immunoglobulins

A 3-year observational study in Japan evaluated the effectiveness of IVIG in 379 patients with corticosteroid-unresponsive BP (mean age: 74.5 years). Improvement rates in IVIG-naive patients were 70.7%, 83.5%, and 84.3% at 15, 30, and 60–90 days, respectively, with significant reductions of corticosteroid doses, and anti-BP180 antibody levels. Approximately 25% of patients required multiple treatment cycles, with a 30-day post-

treatment improvement rate of 88% and complete symptom resolution in 44%. These results support the efficacy of IVIG in treating corticosteroid-unresponsive BP. [38]

Novel target treatments

Rituximab

Rituximab is a chimeric human/mouse glycosylated immunoglobulin (Ig) G1-κ monoclonal antibody, combining murine variable region sequences for both light and heavy chains with human kappa and IgG1 constant region sequences. Rituximab specifically targets the B-lymphocyte transmembrane protein CD20, which is present on normal B cells (excluding stem cells, pro-B cells, and plasma B cells) as well as on most malignant B cells. [39]

Polansky et al. conducted a retrospective study of 20 patients treated with at least one dose of RTX for severe or recalcitrant bullous pemphigoid. They found that 75% (15 patients) achieved remission an average of 169 days after RTX therapy. No RTX-related deaths occurred, and adverse events were significantly fewer. [40]

In a case series by Tovanabutra and Payne, 38 patients with various types of pemphigoid (including BP, mucous membrane pemphigoid, and epidermolysis bullosa acquisita) were treated with RTX. Seventy-six percent (29 patients) reached complete remission after a median of one RTX cycle, and 39% (15 patients) achieved complete remission off therapy after a median of two cycles. BP 180 titers decreased significantly in 13 BP patients. Serious infections occurred in 13% of patients, mostly those on prednisone or additional immunosuppressives. [41]

Dupilumab

Dupilumab, a human monoclonal antibody of the immunoglobulin G4 subclass, acts as an interleukin-4 (IL-4) receptor alpha antagonist, effectively blocking the signaling pathways of both IL-4 and IL-13. [42]

Patients receiving dupilumab showed a more rapid resolution of new blisters, faster tapering of glucocorticoids, reduced healing time, and shorter hospitalizations. Moreover, eosinophil counts and immunoglobulin E levels significantly decreased after two weeks of treatment. Subsequent follow-up studies indicated that dupilumab monotherapy was linked to a reduced recurrence rate. Importantly, no serious adverse effects were reported. [43]

Omalizumab

Omalizumab binds with IgE antibodies and prevents their interaction with FcεRI receptors on mast cells and basophils, thereby inhibiting degranulation and release of mediators of the allergic response. [44]

Between 2014 and 2021 the effectiveness of omalizumab treatment was studied among 100 patients. Complete remission (CR) was attained in 77% of patients, with an additional 9% achieving partial remission. Among those in CR, 11.7% remained in remission without therapy, 57.1% required minimal therapy, and 31.2% needed non-minimal therapy. The relapse rate was 14%, with a median follow-up period of 12 months. Adverse events were reported in four patients. Patients receiving omalizumab doses >300 mg every 4 weeks had similar long-term outcomes to those on doses ≤300 mg, but achieved disease control significantly faster.[45]
The study results suggest that the combination of RTX and OMZ is well tolerated, has the potential to enhance outcomes in patients with refractory BP unresponsive to RTX alone, and may shorten the time required to achieve remission. [46]

Rituximab, omalizumab, and dupilumab have similar clinical benefits for BP patients. However, rituximab resulted in higher recurrence rates, adverse events, and mortality rates. [47]

Nomacopan

Nomacopan, a drug originally derived from tick saliva, has dual functions of sequestering leukotriene B_4 (LTB_4) and inhibiting complement component 5 (C5) activation. [48]

The nonrandomized controlled trial by Sadik et al indicated that a 6-week treatment with nomacopan was well tolerated in patients with bullous pemphigoid. Patients received nomacopan, 90 mg, subcutaneously on day 1 and 30 mg subcutaneously daily until day 42. The cohort had a median age of 75 years and consisted of 5 women and 4 men. Among the participants, 55.6% were experiencing their first episode of bullous pemphigoid, while 44.4% had relapsing disease. Two patients had mild disease, and seven had moderate disease severity. The findings suggest that nomacopan may provide a significant therapeutic benefit for managing this condition. [49]

Avdoralimab

Avdoralimab (IPH5401), a specific anti-C5aR1 monoclonal antibody, has already been credited of a good safety profile in the treatment of solid tumors and rheumatoid arthritis. Experimental data suggest involvement of the C5a–C5aR1 axis in bullous pemphigoid. A phase 2 study evaluated the efficacy and safety of avdoralimab, an anti-C5aR1 antibody, combined with superpotent topical steroids. Patients were randomized to receive either steroids alone or with avdoralimab. At week 12, complete remission was observed in one patient receiving avdoralimab and none in the steroid-only group. No treatment-related adverse events were reported. The study found no added benefit of avdoralimab over steroids alone. [50]

Sutimlimab

Sutimlimab is a humanized monoclonal antibody used to treat cold agglutinin disease (CAD). It is an IgG4 subclass monoclonal antibody that works by inhibiting the classical complement pathway. It does so by binding to the C1s subcomponent of complement protein 1, a serine protease that cleaves C4 and C2, leading to the formation of the C3 convertase. [51]
In a phase 1 trial, the safety and activity of sutimlimab, were evaluated in 10 patients with active or prior bullous pemphigoid. Four weekly infusions of 60 mg/kg effectively inhibited the classical complement pathway, as measured by CH50, in all participants. Partial or complete reduction of C3c deposition at the dermal-epidermal junction (DEJ) was observed in 4 of 5 cases where it was present at baseline. The treatment was generally well-tolerated, with mild to moderate adverse events reported, such as headache and fatigue. [52]

Reslizumab

Reslizumab is a humanized monoclonal antibody targeting interleukin-5 (IL-5).
IL-5 plays a key role in stimulating the production, activation, and maturation of eosinophils. [53]
The study about a male with erythematous bullous eruption, consistent with bullous pemphigoid, showed a potential role for anti-interleukin-5 therapy in BP.
Initial treatment with topical and systemic steroids (methylprednisolone 2 mg/kg/day) led to symptom recurrence upon steroid tapering. On day 29, intravenous reslizumab (3.5 mg/kg) was administered, resulting in rapid improvement of skin lesions. Steroid dosage was reduced to 8 mg/day without symptom worsening after two doses of reslizumab. [54]

Diacerein

Diacerein, an anthraquinone derivative, is a non-steroidal anti-inflammatory drug (NSAID) that works by inhibiting the interleukin-1β system and its associated downstream signaling pathways. [55]

In vitro, diacerein inhibited the reduction of BP180 and the production of proinflammatory cytokines induced by BP autoantibodies, showing therapeutic potential in BP patients.

Yung-Tsu Cho's et al. research indicates that topical diacerein reduced the clinical symptoms which were comparable to those of topical clobetasol. [56]

IL-2 therapy

The results of the new reaserch suggest that low-dose IL-2 therapy is promising for its early onset of response, especially in the first 2 weeks. The rapid increase in Treg cells during the first week may be beneficial for disease control and early steroid reduction. [57]

JAK inhibitors

Currently, there have been successful reports of the treatment of BP with four JAK inhibitors: tofacitinib, baricitinib, upadacitinib, and abrocitinib. Tofacitinib, an oral Janus kinase (JAK) inhibitor, works by suppressing the activation of neutrophils and eosinophils, as well as relieving chronic pruritus through the inhibition of interleukin (IL)-4Rα and JAK1 signaling. [58,59]

Notably, Juczynska et al. observed a significantly higher expression of JAK/STAT proteins in the skin lesions of BP patients compared to controls, suggesting that targeting this signaling pathway could be a promising approach for treating BP. [60]

In Fan report seven patients with bullous pemphigoid who had previously responded to standard therapy experienced relapses upon discontinuation of treatment. Three of these patients had failed a 3-month course of dupilumab and developed complications due to prior systemic glucocorticoid (sGC) use. Prior to starting tofacitinib, the average disease duration was 15.3 months. All patients exhibited elevated BP180-NC16A-specific IgG levels, and five had increased eosinophil counts. Key cytokines such as IL-6, tumor necrosis factor (TNF)-α, and IL-17 were also monitored. All patients were treated with tofacitinib at 5 mg twice daily. In addition, four patients received 20-40 mg of sGC daily, while three patients were given 10-30 g of topical corticosteroids (tGC) daily as an initial dose. The results suggest that tofacitinib

may be a safe and effective option for reducing inflammation and relieving pruritus in BP patients. [61]

In the Case report by Xiao et al Baricitinib at a daily oral dose of 4 mg resulted in a complete remission of BP in 24 weeks without any adverse effects. [62]

Plasmapheresis therapy

Plasmapheresis, including plasma exchange (PE) and double filtration plasmapheresis (DFPP), is a treatment option for severe or refractory cases of bullous pemphigoid. In therapeutic PE, anticoagulated blood is processed through a device that separates plasma from other blood components. The plasma is replaced with a solution such as albumin, plasma, or a mix of crystalloid and colloid solutions, and the remaining blood elements are reinfused. DFPP uses specialized filters to remove pathogenic substances from plasma based on their molecular size and configuration. This process eliminates harmful autoantibodies, immune complexes, and cytokines. Plasmapheresis, combined with glucocorticosteroids and/or immunosuppressive agents, has been associated with reduced anti-BP180 antibody levels, alleviation of pruritus, and resolution of bullae in severe cases. [63,64]

Conclusions

Bullous pemphigoid is a complex autoimmune blistering disease with multifaceted pathogenesis, diagnostic criteria, and treatment options.

Advancements in understanding BP's underlying mechanisms—such as the roles of IgG and IgE autoantibodies, complement activation, and type 2 inflammation—have expanded the diagnostic and therapeutic landscape, but the role of neuroimmune interactions in BP pathogenesis remains unclear.

Management strategies are evolving to balance efficacy with patient safety, especially given the vulnerability of the predominantly elderly BP population. High-potency topical corticosteroids remain first-line therapy due to their effectiveness and reduced systemic risks. Systemic corticosteroids and steroid-sparing agents, including immunosuppressants like azathioprine, methotrexate, and mycophenolate mofetil, provide alternatives for severe or resistant cases. Novel therapies targeting specific pathways, such as dupilumab and rituximab, show promise in refractory cases, emphasizing the growing role of biologics in BP treatment.

Omalizumab demonstrates high efficacy in achieving remission, with minimal adverse effects, making it a promising option for refractory BP, particularly when combined with rituximab. Nomacopan, while showing potential in reducing disease activity through dual leukotriene B4 sequestration and C5 inhibition, requires further validation in larger cohorts.

Experimental treatments like avdoralimab and sutimlimab highlight the emerging focus on complement system modulation, though their clinical efficacy over standard therapies remains unclear. Reslizumab and diacerein offer targeted anti-inflammatory benefits, emphasizing eosinophil regulation and cytokine inhibition, respectively, and have shown encouraging results in steroid-sparing strategies.

Low-dose IL-2 therapy and JAK inhibitors provide innovative approaches by enhancing regulatory T cells and inhibiting key inflammatory signaling pathways, with promising outcomes in disease control and symptom alleviation.

These findings underscore the importance of personalized therapeutic strategies, balancing efficacy, safety, and the potential for steroid reduction, while paving the way for future research to optimize BP management.

Authors contributions

Conceptualization, Julia Nowak and Katarzyna Doman; methodology, Julia Nowak and Michał Jakub Cioch; software, Aleksandra Woźniak and Marcin Mycyk; check, Agnieszka Najdek and Daria Oleksy; formal analysis, Dawid Komada and Kamil Hermanowicz; investigation, Dawid Komada and Marcin Mycyk; resources, Julia Nowak and Katarzyna Doman; data curation, Urszula Kaczmarska and Aleksandra Woźniak; writing – rough preparation, Julia Nowak; writing - review and editing, Julia Nowak; visualization,Agnieszka Najdek Kamil Hermanowicz; supervision, Urszula Kaczmarska and Michał Jakub Cioch project administration, Julia Nowak.

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All authors declare that they have no conflicts of interest.

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