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BULLOUS PEMPHIGOID: CURRENT AND EMERGING THERAPIES

Bullous pemphigoid (BP) is the most common autoimmune blistering condition. It preferentially affects the elderly population between the ages of 60 to 80. Younger populations can be afflicted such as in cases involving drug-induced bullous pemphigoid and, rarely, in childhood bullous pemphigoid. The incidence of BP has been rising recently, partly due to increased overall life expectancy.

The pathophysiology of BP involves IgG circulating autoantibodies targeting components of the hemidesmosomes at the basement membrane zone involving BP230 (BPAG1) and BP180 (BPAG2, type XVII collagen). Clinically, BP is characterized by generalized pruritus followed by tense vesiculobullae that commonly present on erythematous or urticarial base (**Figure 1**). The non-bullous phase of BP presents as eczematous patches and urticarial wheals. Vesicles and bullae may appear hemorrhagic or serous. Oral mucosal involvement is seen in 10-30% of patients.

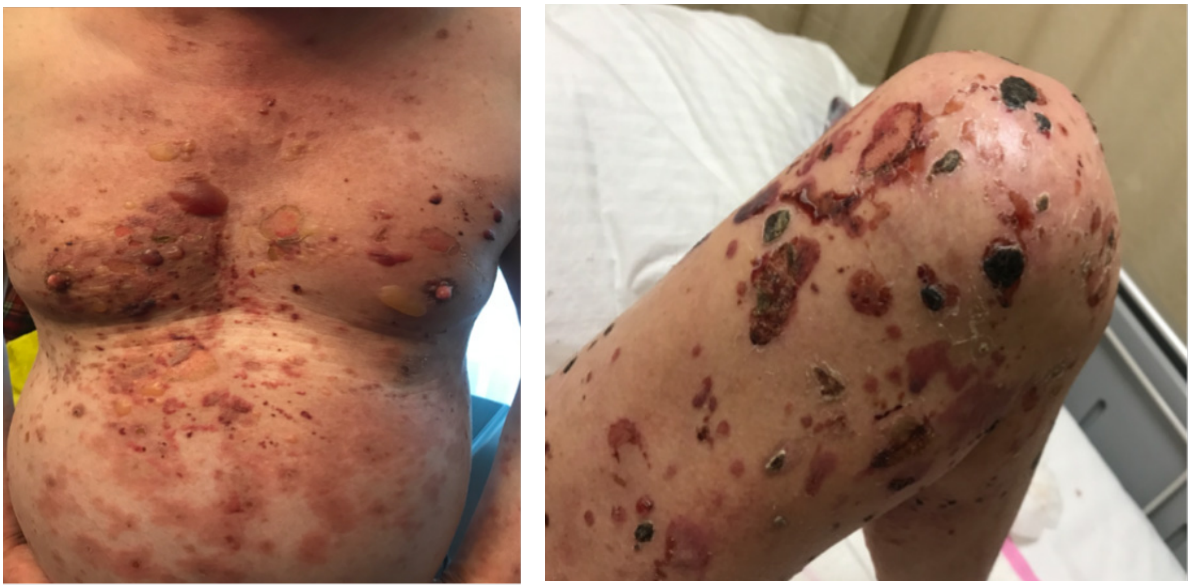

Figure 1: *Patient with bullous pemphigoid with tense bullae on an urticarial base and serous and hemorrhagic crusting; photos courtesy of Bahar Bahrani, MD*

The objective of treatment in BP is to halt disease development, heal existing blisters and to reduce pruritus. Rapid and effective treatment is critical in cases of widespread disease involvement. Management of BP should be personalized for each patient depending on the severity of the disease as well as the patient's age, comorbidities and preferences. Elderly patients are more likely to have multiple co-existing medical conditions where polypharmacy may be a concern. Careful consideration should be given to drug interactions and medication side effects when treating this population to avoid unnecessary harm.

The management of BP is usually classified into mild/localized and severe/extensive disease based on development of new blisters per day but can also be based on body surface area involvement. Disease severity can be further classified based on the subjective Bullous Pemphigoid Disease Area Index (BPDAI) and objective Bullous Pemphigoid Disease Area Index.[1] A laddered approach to treatment depending on severity is recommended (**Figure 2**), however treatment recommendations vary widely amongst various consensus guidelines (**Table 1**). Despite various therapeutic options available for the treatment of BP, there is a lack of large randomized clinical trials to support strong evidence of these treatments (**Figure 3**). This is likely due to the low prevalence of the disease and underpowered studies. Outlined below are the current and emerging therapeutic options for BP as well the level of evidence to support their use in BP.

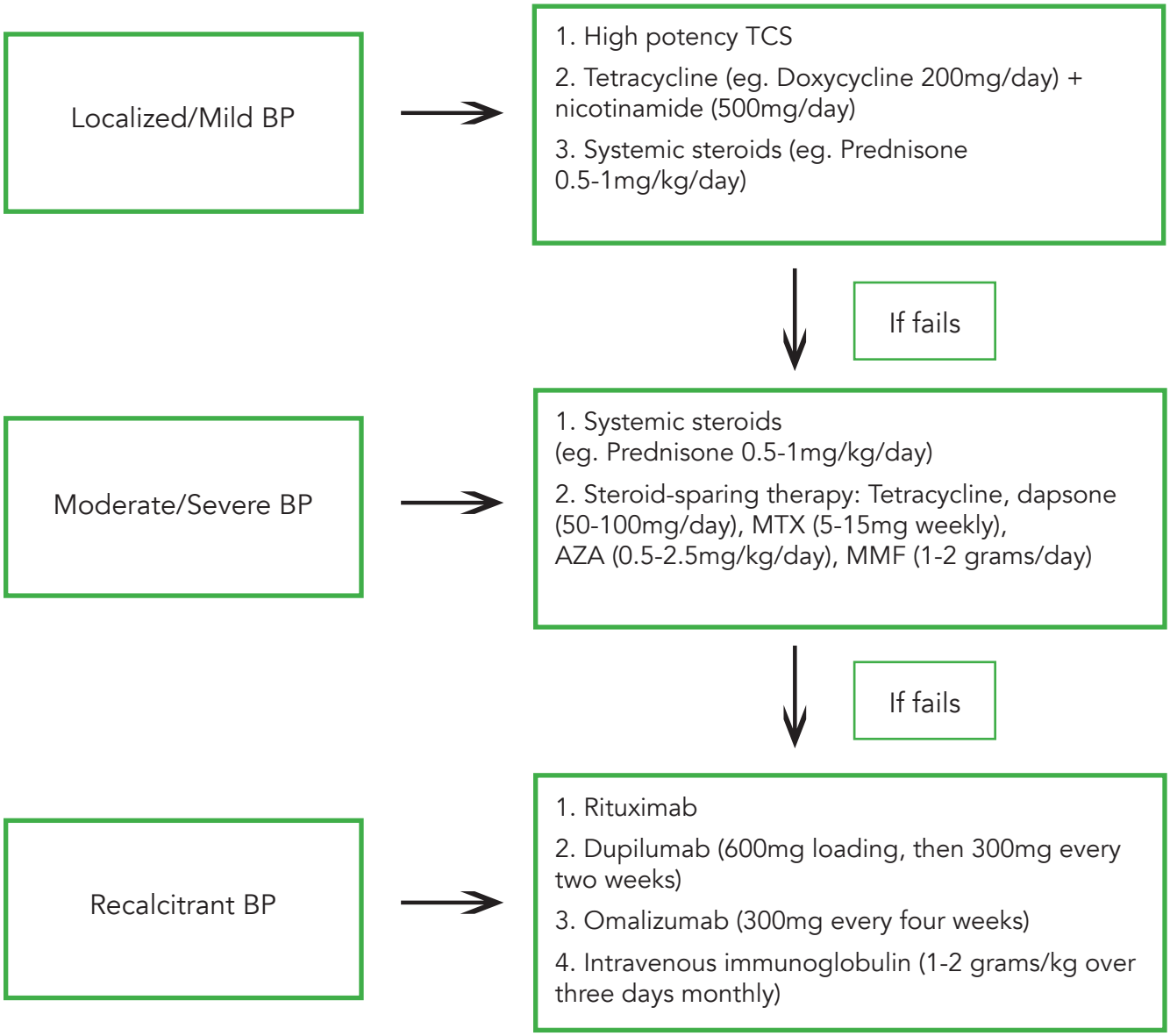

Figure 2. *Algorithm for treatment of bullous pemphigoid; adapted from Pratasava et al.*[2]

	First Line	Second Line	Adjuvants	Refractory
Association of the Scientific Medical Societies in Germany	Mild: TCS Moderate: TCS + Systemic steroids Severe: TCS + systemic steroids +/- listed adjuvants; monotherapy with doxycycline +/- nicotinamide, dapsone, MTX	Same agents listed in adjuvants and refractory	AZA, dapsone, MMF, MTX, doxycycline +/- nicotinamide	IVIG, immunoadsorption, plasma exchange, rituximab, cyclophosphamide, anti-IgE monoclonal antibody
Brazilian Society of Dermatology	Localized: TCS Extensive: Systemic steroids + TCS	Extensive: Same agents listed in adjuvants Mucosal: Dapsone	Oxytetracyline, doxycycline +/- nicotinamide, AZA, MMF, MTX, dapsone, chlorambucil	Rituximab, anti-IgE monoclonal antibody, IVIG, plasma exchange, cyclophosphamide
British Association of Dermatologists	Mild: TCS, systemic steroids +/- TCS, anti-inflammatory antibiotics +/- nicotinamide Moderate-Severe: Systemic steroids + TCS, TCS, anti-inflammatory antibiotics +/- nicotinamide	Switch or addition of adjuvants	Systemic steroids +/- TCS, anti-inflammatory antibiotics +/- nicotinamide, AZA, MTX, dapsone, chlorambucil, MMF	IVIG, cyclophosphamide, plasma exchange
Cutaneous Immunology Group of the Italian Society of Medical Dermatology	Mild: TCS Generalized: Systemic steroids +/- TCS	Mild: Systemic steroids +/- tetracycline + nicotinamide, dapsone Generalized: Combine or introduce adjuvants	AZA, MMF, tetracycline + nicotinamide, MTX, chlorambucil	IVIG, immunoadsorption, rituximab, anti-IgE monoclonal antibody, cyclophosphamide, plasma exchange
European Dermatology Forum & European Academy of Dermatology and Venereology	Mild: TCS Generalized: Systemic steroids +/- TCS	Mild: Systemic steroids, but can consider tetracycline + nicotinamide Generalized: Combine or introduce adjuvants	AZA, MMF, tetracycline + nicotinamide, MTX, chlorambucil	Rituximab, anti-IgE monoclonal antibody, IVIG, immunoadsorption, cyclophosphamide, plasma exchange
French Society of Dermatology	Any severity: TCS	Localized: MTX Mild: MTX +/- tetracycline Extensive: Systemic steroids +/- AZA, or MMF, MTX	AZA, MMF, MTX, tetracycline	Same as adjuvants
Japanese Dermatological Association	Mild: TCS + adjuvants Moderate/severe: Systemic steroids + TCS +/- tetracycline/ minocycline + nicotinamide, dapsone	Mild: Manage as severe Moderate/severe: Combine with adjuvants	Mild: TCS/ minocycline + nicotinamide, systemic steroids Moderate/severe: AZA, CsA, mizoribine, cyclophosphamide, dapsone, MMF, MTX, pulse IV steroids, IVIG	Cyclophosphamide IV pulse, plasma exchange, rituximab

Table 1: *Guideline treatment recommendations for bullous pemphigoid; adapted from Patel et al.* [2]

AZA azathioprine, CsA cyclosporine, IVIG intravenous immunoglobulin, MMF mycophenolate mofetil, MTX methotrexate, TCS topical corticosteroid

Topical Steroids

In mild disease, first-line treatment is clobetasol propionate ointment or cream.[5] A landmark French study compared the use of topical steroids (clobetasol propionate 40 g/day) versus oral prednisone (0.5 mg per kilogram of body weight per day for those with moderate disease and 1 mg per kilogram per day for those with extensive disease).[6] Researchers found that topical steroids were associated with improved overall survival at 1 year (76% vs 58%, respectively), and had fewer severe complications (29% vs. 54%, respectively) in patients with extensive disease. In the cohort of patients with moderate bullous pemphigoid, there were no significant differences between the topical-corticosteroid group and the oral-prednisone group in terms of overall survival, the rate of control at three weeks, or the incidence of severe complications. Another study compared clobetasol propionate cream 20g b.i.d. (standard regimen) to 10-30 g/day (mild regimen) depending on severity.[7]
The mean cumulative dose of steroid cream was 70% less in the mild regimen group, while the time to regression as well as relapse rate in both groups were the same. The standard regimen group had higher numbers of reported side effects of diabetes, cardiovascular disorders, severe infections, cutaneous atrophy, striae and purpura. There are some practical limitations to the use of topical steroids, as elderly patients likely require assistance to apply topicals on large body surface areas.

Topical Tacrolimus

Topical immunomodulators have been reported to be effective in localized and mild generalized BP; however data is limited to case reports. Three to five grams of tacrolimus 0.1% daily can help in reduction of oral steroids and improvement in disease as early as 2 weeks.[8] Side effects include burning and local irritation and cost may also limit the use of this topical agent. Nonetheless, it can be used as an alternative in localized disease with the advantage of not causing steroid atrophy.

Systemic Steroids

Systemic steroids are considered the mainstay treatment for severe generalized disease. Prednisone at a dose of 0.5-1 mg/kg/day should be initiated for severe systemic disease, with a dose of 0.5 mg/kg usually sufficient for mild disease.[3] Greater than 1mg/kg/day of systemic steroids is rarely required. A randomized multicentre study compared prednisone dosed at 0.75 mg/kg/day versus 1.25 mg/kg/day and found that the outcomes in these groups were not statistically significant.[9] Intravenous systemic steroids do not confer any benefit over oral systemic steroids.[10]

Tetracycline and Nicotinamide

The mechanism by which tetracycline works in bullous pemphigoid is via the inhibition of chemotaxis of neutrophils and eosinophils. Nicotinamide decreases the inflammatory pathway by inhibiting phosphodiesterase, inhibition of histamine release and inhibition of chemotaxis. A randomized prospective study evaluating the efficacy of doxycycline vs prednisolone as initial therapy showed that doxycycline was non-inferior to prednisolone in disease control.[12] Patients who received doxycycline also had fewer severe adverse events. These results may suggest that tetracycline is more appropriate in patients with comorbidities and in those who have contraindications to systemic steroids. A retrospective study compared tetracycline and nicotinamide combined with clobetasol cream vs prednisone 0.5 mg/kg, with the former

Mild and/or localized disease
Super potent topical corticosteroids
Oral corticosteroids
Minocycline, doxycycline or tetracycline +/- nicotinamide
Topical immunomodulators
Dapsone and sulfonamides
Erythromycin
Penicillin
Extensive/persistent disease
Super potent topical corticosteroids
Oral corticosteroids
Azathioprine
Mycophenolate mofetil
Methotrexate
Intravenous immunoglobulin
Rituximab
Omalizumab
Dupilumab
Plasma exchange
Immunoadsorption
Cyclophosphamide
Chlorambucil
Legend
Prospective Controlled Trial
Retrospective study or large case series
Small case series/individual case reports

Figure 3. *Therapies for mild and extensive bullous pemphigoid with corresponding levels of evidence* [4]

having higher efficacy and better survival rates.[13] A meta-analysis showed that tetracycline plus nicotinamide had better outcomes than either tetracycline alone or systemic steroids.[14] It is important to note that doxycycline is renally cleared and that in patients with renal impairment, minocycline should be used as an alternative.

Azathioprine

Azathioprine is a commonly-used steroid-sparing agent in BP, and is administered as an adjuvant treatment in doses up to 2.5 mg/kg/day. Despite this, the evidence to support the use of azathioprine is limited and conflicting. One small RCT showed that the use of azathioprine resulted in a 45% reduction in cumulative prednisolone dose over a 3-year period, and supported its use in the management of BP.[15] Another study revealed that prednisolone compared with prednisolone plus azathioprine was not associated with a difference in remission rates.[16] In this same study there was also an increased number of adverse events in the azathioprine group, which may have been the result of no azathioprine dose adjustments based on thiopurine methyl transferase (TPMT) levels. It is also important to note that a normal TPMT does not exclude the possibility of myelotoxicity, and regular monitoring of blood counts is critical.

Methotrexate

There are no controlled trials studying the use of methotrexate in BP. Several case series have revealed that low-dose methotrexate either alone or in combination with topical or systemic steroids may work in controlling BP.[17-20] Doses of methotrexate ranging from 5-15 mg/wk have been reported to be effective.[11] Methotrexate is excreted renally, which should be taken into consideration especially in elderly patients in whom renal impairment or dysfunction is a concern. This may explain why low doses of methotrexate are often sufficient in BP patients. Folic acid at a dose of 5 mg on non-methotrexate treatment days is recommended to reduce adverse effects, however this has not been adequately studied.

Mycophenolate mofetil

Mycophenolate mofetil is a prodrug of mycophenolic acid and is an inhibitor of the purine synthesis pathway in T and B cells. Several studies have shown that mycophenolate mofetil is effective, either alone or in combination with steroids, for the treatment of BP.[21-23] A study comparing mycophenolate mofetil dosed at 1g b.i.d. and azathioprine dosed at 2 mg/kg daily showed that both drugs had 100% remission when combined with systemic steroids.[24] A similar number of relapses and adverse events were seen amongst both groups, however, the average time to complete remission was shorter in the azathioprine group.

Dapsone

Dapsone is an antimicrobial belonging to the sulfonamide class of antibiotics with anti-inflammatory properties. Doses of 50-200 mg daily are commonly administered in BP. The time to response in patients receiving dapsone is slower compared to patients taking steroids. Three retrospective case series involving the use of dapsone demonstrated that the response rate was around 45%.[25-27] There is no strong correlation between the density of neutrophilic infiltration on pathology and response to dapsone.[25] Dapsone must be used with caution in elderly patients and should be utilized if other treatments are contraindicated or ineffective in this population. Dapsone should be started at 50 mg daily and be increased by 50 mg every 2 weeks to a maximum of 150-200 mg daily. Frequent blood work monitoring is required in the first few months of treatment.

Rituximab

Rituximab is a monoclonal antibody targeting CD20+ mature B cells, which causes B-cell depletion and a reduction in antibody production. Recently, rituximab has been used for the treatment of refractory BP. The dose of rituximab for BP has not been established, however most clinical diseases use the non-Hodgkin lymphoma or rheumatoid arthritis dosing, which is an intravenous infusion of 375 mg/m^2/week for four weeks or 1000 mg/week for two consecutive weeks, respectively. Rituximab may achieve only temporary remission of BP, and as such a maintenance treatment may be required. Improvement of BP is usually seen after 4 weeks of treatment with rituximab and complete remission of BP has been estimated at 65-70% in recent studies.[28]

Dupilumab

Dupilumab is a fully human monoclonal antibody that inhibits IL-4α subunit that is shared by IL-4 and IL-13 receptors. The pathogenesis of BP involves circulating IgG autoantibodies to BP180 and BP230, but IgE autoantibodies have also been identified which contribute to the Th2 regulation. Th2 cells that produce IL-4 and IL-13 are increased in BP patients. Given this mechanism, dupilumab has been considered as a possible treatment in BP.[29] A small case series reviewed the use of dupilumab in 13 elderly patients with BP recalcitrant to traditional immunosuppressants. Results demonstrated that 12/13 (92%) had disease clearance or a satisfactory response, 7/13 (54%) obtained clearance defined as no bullae or pruritus, and 5/13 (38%) obtained clearance with the addition of an immunosuppressive.[30] A large portion of the patients that developed clearance received dupilumab more often than every two weeks.

Omalizumab

Omalizumab is a humanized monoclonal antibody that binds free serum immunoglobulin E (IgE) and prevents it from binding to the receptor on mast cells and basophils. It works in BP by

preventing the interaction of IgE with FcεRI receptors on mast cells and other effector cells to reduce the release of inflammatory mediators. Omalizumab has been used in refractory cases of BP. The dose of omalizumab is based on its use in chronic urticaria and asthma, and most patients benefit from subcutaneous injection of 300 mg every 4 weeks. The use of omalizumab in BP, has led to a reduction in itching, blister formation and eosinophil levels as early as a few weeks within initiation of treatment. Peripheral eosinophil levels have been linked to a positive response with omalizumab.[31]

IVIG

Clinical response to the use of IVIG in BP is often rapid but short-lasting, thus requiring repeat infusions or the addition of an adjunctive therapy. The treatment regimen for BP is typically 2 g/kg administered in equally-divided doses over 3 days. Treatment is repeated every 4 weeks until remission is achieved, after which interval cycles are increased gradually. In a small retrospective study involving 15 patients, IVIG was administered to patients with steroid-dependence and treatment-related side effects.[32] The use of IVIG allowed for the tapering of prednisone in all patients within 1-5 months, and remission was maintained for 17-27 months thereafter. The mean number of cycles of IVIG used in this retrospective study was fifteen. IVIG can be effective for the treatment of BP, however due to cost barriers it should be reserved for refractory patients, cases requiring rapid control, and when contraindications to other treatments are present.

Other

Other treatment options for BP include cyclophosphamide, chlorambucil, plasma exchange and apheresis. Due to their severe toxic side effect profiles, cyclophosphamide and chlorambucil should only be used in extremely recalcitrant cases which are refractory to conventional immunosuppressants. The role of plasma exchange in the management of BP is not known, as results have been mixed with one randomized controlled trial (RCT) documenting a steroid-sparing effect whereas another RCT not showing a benefit.[33, 16] Cyclosporine has no good evidence supporting its use in BP and is not recommended as routine treatment.[10]

Emerging Treatment Options

The current mainstay treatment for BP includes the use of steroids and traditional immunosuppressive therapies. To date there have been no approved biologics for BP, however increased understanding of the pathophysiology of the disease gives rise to various biomarker targets for potential treatment. There are several emerging therapies that are currently undergoing clinical trials (**Table 2**).

Biologic	Target	Mechanism	Clinical Trial Studies In progress
Omalizumab	Antibodies	Humanized monoclonal antibody that targets free IgE preventing binding on mast cells and basophils	Phase 3
Dupilumab	Th2 Axis	Monoclonal antibody that inhibits IL-4α subunit that is shared by IL-4 and IL-13 receptors	Phase 3
Sutimlimab	Complements	Humanized IgG_4 monoclonal antibody inhibits the C1s complements in the classical complement pathway	Phase 1
Avdoralimab	Complements	Antibody against C5aR1, which inhibits BP180 IgG-induced pathogenicity	Phase 2
Bertilimumab	Eosinophils	Human monoclonal antibody targeting eotaxin-1 (CCL-11) which is involved in the recruitment of eosinophils from peripheral circulation to skin	Phase 2
Benralizumab	Eosinophils	Humanized IgG1 κ monoclonal antibody against IL-5Rα subunit which blocks downstream of IL-5 leading to decrease eosinophils and basophils	Phase 3
Ustekinumab	Th17 Axis	Humanized monoclonal antibody targeting p40 shared subunit of IL-12 and IL-23	Phase 2
Tildrakizumab	Th17 Axis	Humanized monoclonal antibody targeting p19 subunit of IL-23	Phase 1

Table 2: *New emerging biologic therapies undergoing clinical trials for the treatment of BP*[34]

Practical Management

In mild BP disease, first line therapy should remain potent topical steroids. In severe or generalized cases, systemic steroids with the addition of an adjuvant therapy should be considered. Choice of adjuvant therapy should be based on the severity of the disease, underlying medical comorbidities and patient preference. In severe cases, adjuvant therapy should be started with or shortly after systemic steroids to allow for the slow onset of action of this therapy, followed by the gradual tapering of steroids once clinical response has been maintained. First line adjuvant therapy can be initiated with anti-inflammatory antibiotics from the tetracycline family with or without niacinamide. In patients who fail this regimen, low dose methotrexate can be used. Subsequent therapeutic regimens may include the use of mycophenolate mofetil or azathioprine. Careful consideration should be made with respect to methotrexate and doxycycline in renally impaired patients. It should be noted that mycophenolate mofetil causes increased infections, whereas azathioprine is more likely to cause hepatotoxicity. Treatments for refractory cases may include rituximab and IVIG, although cost may be a barrier to access.

Conclusion

Potent topical steroids should be the mainstay of treatment in localized disease, and oral steroids must be used cautiously in elderly patients with BP. Adjuvant therapies can reduce the cumulative steroid dose required to keep the disease quiescent. However, steroid-sparing immunosuppressants may also lead to increased morbidity and mortality due to their unfavourable side effects. Larger randomized clinical trials are necessary to study the efficacy of the treatment agents in BP.

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