doi.org/10.58931/cdt.2025.61133

ABOUT THE AUTHOR

Bahar Bahrani, MD, FRCPC

Dr. Bahrani is a fellow of the Royal College of Physicians and Surgeons of Canada in dermatology and a Diplomate of the American Board of Dermatology. She completed her medical school training at the University of Saskatchewan and did her dermatology residency at University of Toronto. She previously practiced as a Clinical Assistant Professor at Duke University in Durham, North Carolina. Dr. Bahrani is currently an Assistant Professor in the Department of Dermatology and Skin Science at the University of British Columbia. She directs the autoimmune blistering disease clinic at St. Paul's Hospital in Vancouver.

Affiliations: Assistant Professor, Department of Dermatology and Skin Science
University of British Columbia

Review of Pemphigus Vulgaris Management

Bahar Bahrani, MD, FRCPC

Introduction

Pemphigus Vulgaris (PV) is an autoimmune blistering disease that is characterized by painful erosions and flaccid blisters involving the mucous membranes and skin (**Figure 1**). The production of pathogenic immunoglobulin autoantibodies, mainly IgG4, against the desmosomal cadherins desmoglein 1 (Dsg-1) and desmoglein 3 (Dsg-3), lead to the loss of epidermal keratinocyte adhesion. In the mucosal dominant type, Dsg-3 antibodies are present, while in the mucocutaneous type, antibodies against both desmoglein 1 and 3 are found. Diagnosing PV requires compatible clinical features, histopathological examination of the involved skin, and the detection of autoantibodies by indirect immunofluorescence of non-affected peri-lesional skin. The pemphigus disease area index (PDAI) and the autoimmune bullous skin disorder intensity score (ABSIS) provide a standardized assessment of disease extent and response to treatment.

A treatment algorithm has been proposed for PV (**Figure 2** and **Figure 3**). In addition, supportive management is also important (**Table 1**).

Treatment

Systemic Steroids

Systemic steroids play an important role in the initial treatment of PV due to their high efficacy and ability for achieving rapid control. Prednisone is the systemic steroid therapy of choice, with doses ranging from 0.5–1 mg/kg/day.[1] Typically, mild PV is treated with 0.5 mg/kg/day, while moderate to severe PV is treated with 1 mg/kg/day, with a usual maximum of 60 mg/day. In mild PV <5% of the total body surface is involved, and there are no oral lesions or only mild oral lesions that do not impair food intake or require topical analgesics. In moderate-to-severe PV >5% of the body surface area is involved, with multiple mucosal

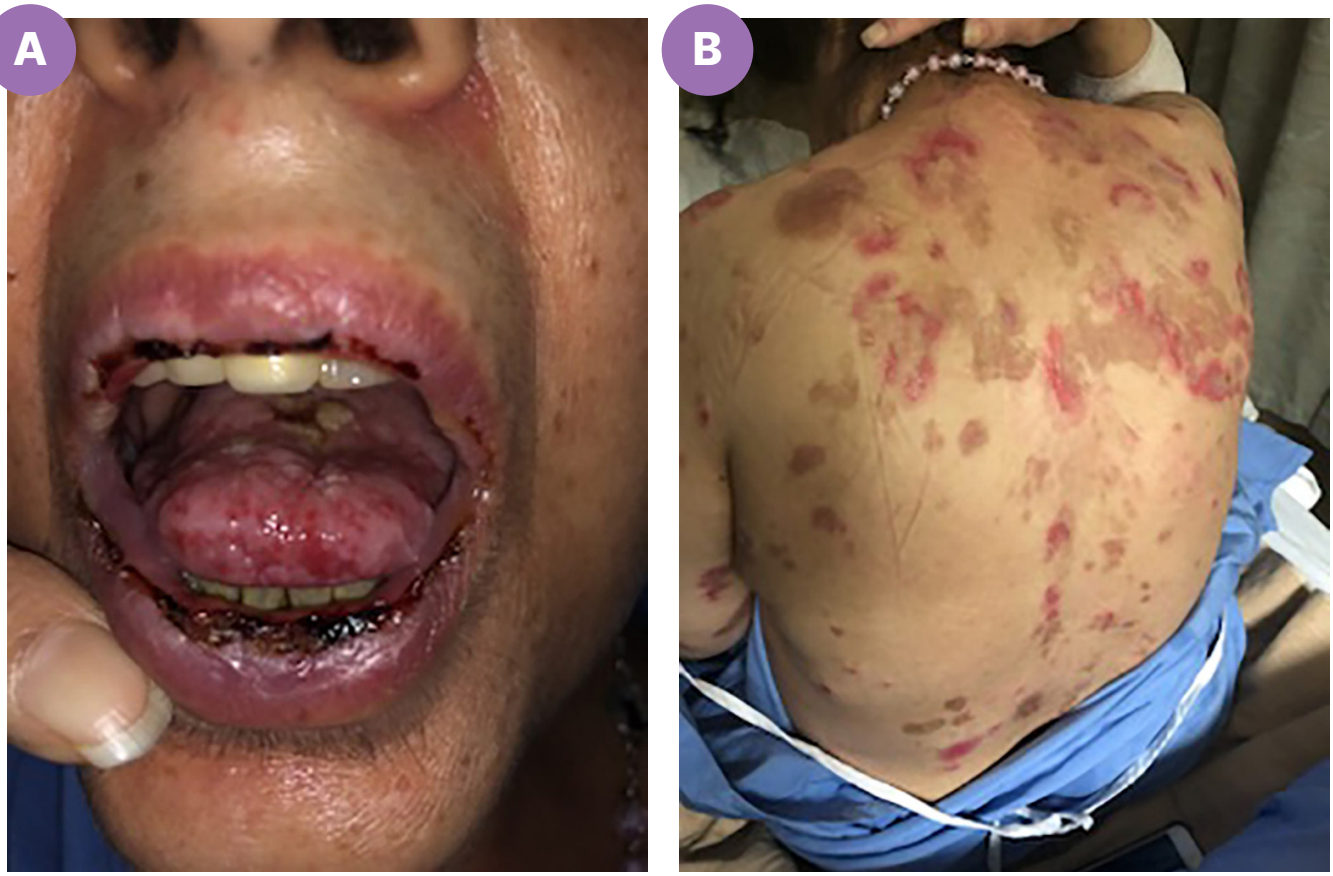

Figure 1. A) Erosions on the tongue and hemorrhagic crust on the lips are observed in a patient with oral pemphigus vulgaris. **B)** Superficial erosions and post-inflammatory hyperpigmentation are observed on the back and arms of a patient with cutaneous pemphigus vulgaris; *courtesy of Bahar Bahrani, M.D., FRCPC.*.

sites, severe oral lesions, dysphagia, weight loss, and significant pain. In the majority of patients, blisters cease within 2–3 weeks and full disease control is achieved within 6–8 weeks.[2] If there is no response to oral steroids after 3–4 weeks, intravenous pulse therapy with 0.5-1 g/day methylprednisolone for 3–5 consecutive days can be added.[3] This treatment requires admission to hospital, as continuous cardiac monitoring is needed.

Steroid therapy can be tapered once there is cessation of new blister formation and established blisters have healed by approximately 80%. The objective is to reduce the steroid dosage to the lowest level that maintains good disease control. Dose reduction should occur in a stepwise fashion, however, there is no standardized approach to this. One proposed regimen is to reduce the dosage from 1 mg/kg to 0.75 mg/kg once no new lesions occur for 1 week, then to 0.5 mg/kg if no new lesions occur for at least 1 week, then to 30 mg if no new lesions are seen for at least 2 weeks. From that point the dosage can be lowered by 2.5–5 mg every 2 weeks until it reaches zero. Another well-described tapering plan is to reduce the dose by 25% every 2 weeks until reaching a dose of 20 mg per day, then decreasing by 2.5 mg per week until reaching 10 mg per day, and decreasing by 1 mg per day thereafter.[4] There are serious potential side effects associated with long-term use of prednisone that include infection, osteoporosis, hyperglycemia, hypertension, and suppression of the adrenal glands.

Rituximab

Rituximab is a monoclonal antibody targeting CD20 on mature B cells, which causes B-cell depletion and reduced antibody production. The preferred initial treatment for PV is a combination of rituximab and prednisone. However, the high

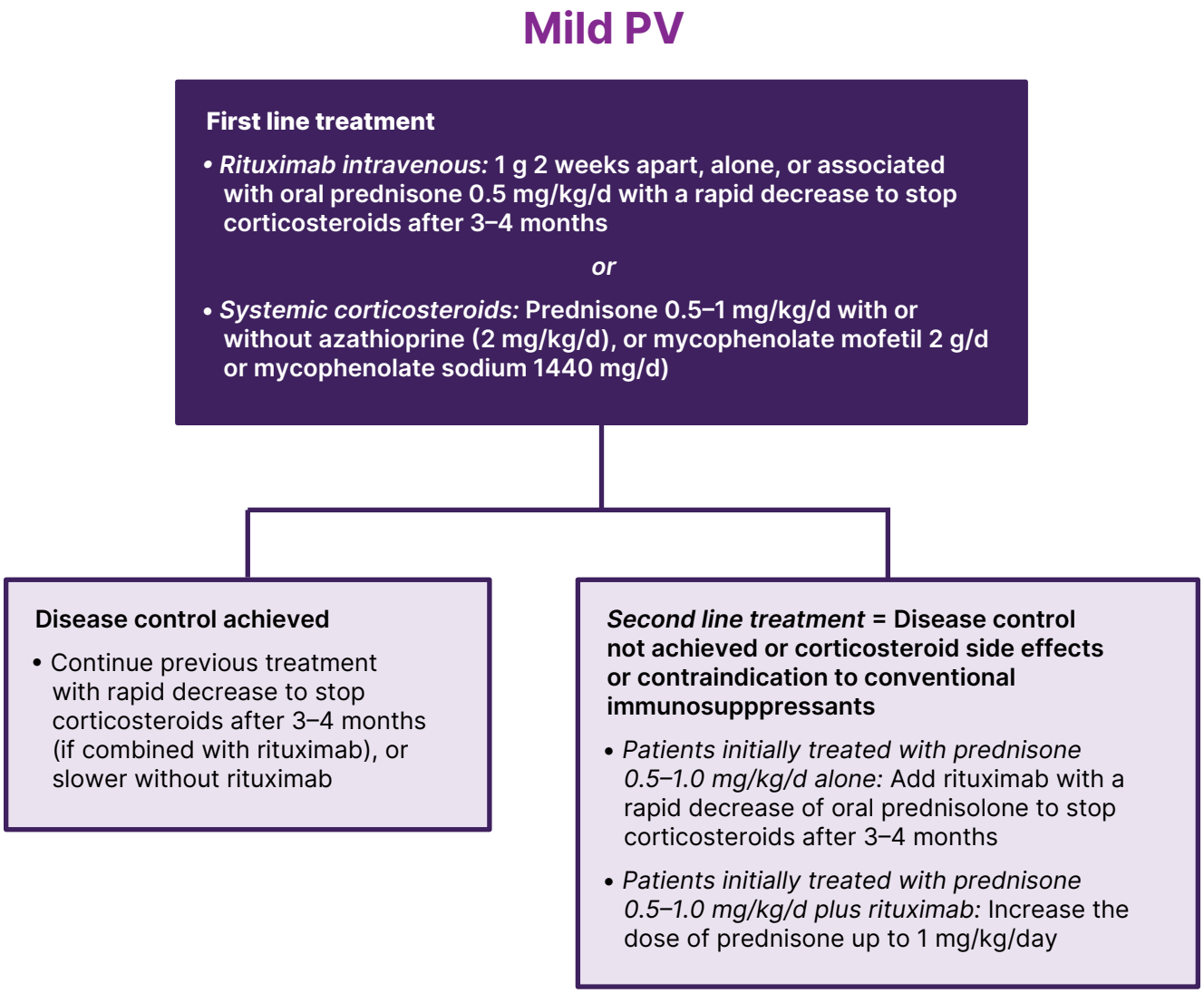

Figure 2. Treatment algorithm for mild pemphigus vulgaris; *adapted from Joly 2020.*[3]

cost and limited availability of rituximab can restrict its use. When rituximab therapy is not possible, prednisone and adjuvant mycophenolate mofetil or azathioprine is recommended.

A study compared 2 treatment regimens with rituximab (1000 mg on days 1 and 14, then 500 mg at 12 and 18 months) plus prednisone (0.5 mg/kg/d for moderate disease and 1 mg/kg for severe disease) tapered over 3–6 months, or prednisone alone (1 mg/kg/day for moderate disease and 1.5 mg/kg/day for severe disease) tapered over 12–18 months. A much larger proportion of patients receiving rituximab and prednisone achieved clinical remission off therapy, reached complete remission much sooner, and experienced less frequent adverse events.[5]

In a randomized trial that compared rituximab plus prednisone versus mycophenolate mofetil plus prednisone, the rituximab/prednisone combination was superior.[6] This study showed a higher likelihood of achieving sustained complete remission, lower dependence on oral steroids, and reduced disease flares in patients with moderate to severe PV in the rituximab/prednisone group. While rituximab has not been directly compared

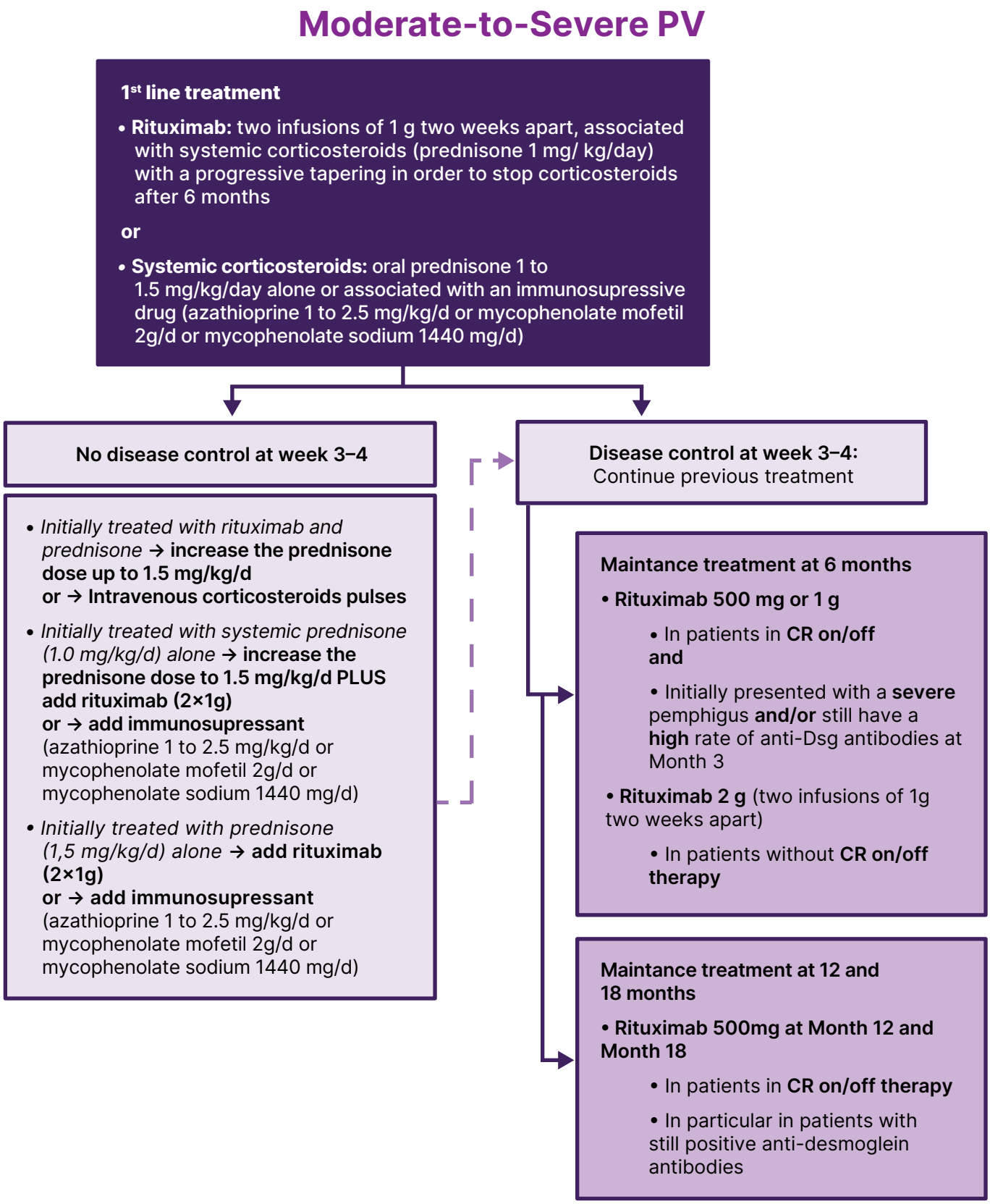

Figure 3. Treatment algorithm for moderate-to-severe pemphigus vulgaris; *adapted from Joly 2020.*[3]

Supportive Care	
Oral symptoms	
Oral hygiene	• Regular brushing with a soft-bristle brush • Bland toothpaste • Daily flossing • Regular professional dental cleaning
Avoidance of certain foods	• Avoid spicy, hot, sharp, or abrasive foods
Topical Anesthetics	• Lidocaine 2% solution or gel as needed
Topical anti-inflammatory therapies	• High-potency topical corticosteroids (fluocinonide or clobetasol in ointment or gel) twice a day as needed • Steroids mouthwash (dexamethasone 0.5 mg/5 ml or prednisolone 5 mg/5 mL) 2–3 times a day to swish and spit as needed • Intralesional triamcinolone acetonide to help with isolated persistent lesions • Tacrolimus 0.1% ointment twice a day as needed
Treatment of Candida	• Nystatin swish and spit or fluconazole
Skin Symptoms	
Wound care	• Erosions should be covered with bland emollient (e.g. petrolatum) +/- non-adhesive wound care dressing
Anti-inflammatory therapies	• High-potency topical corticosteroids (fluocinonide or clobetasol in ointment) twice a day as needed • Intralesional triamcinolone acetonide to help with isolated persistent lesions • Tacrolimus 0.1% ointment twice a day as needed
Treatment of secondary infections	• Treat for secondary infections with herpes simplex virus and bacterial infections

Table 1. Supportive adjunct therapies in pemphigus vulgaris; *courtesy of Bahar Bahrani, MD, FRCPC*.

to azathioprine, a meta-analysis suggests a greater likelihood of disease remission and lower cumulative steroid doses with rituximab.[7]

Rituximab is administered as a 1000 mg intravenous solution, given 2 weeks apart, followed by periodic maintenance doses as needed. Typically, steroid therapy begins before rituximab, as the effects of rituximab may not appear until 8–12 weeks after therapy. The major risks of rituximab are infusion reactions and infections. Progressive multifocal leukoencephalopathy is a rare complication that has been reported in patients treated with rituximab for other indications.

Azathioprine

Azathioprine downregulates purine metabolism and reduces the activity of T and B lymphocytes. Reduced dosing is recommended for patients with low or intermediate

thiopurine-methyltransferase (TPMT) activity and is not advised for those with absent TPMT activity.[3] The usual starting dose is 1 mg/kg (ideal body weight) per day and can increase by increments of 0.5 mg/kg to reach a maximum of 2.5 mg/kg for treating PV. It is important to note that a normal TPMT level does not exclude the possibility of myelotoxicity, thus, regular monitoring of blood counts is critical. Severe adverse effects include pancytopenia and hepatotoxicity.

The findings from studies evaluating the effectiveness of azathioprine have been conflicting. A randomized trial compared the use of prednisolone 2 mg/kg/day (maximum 120 mg per day) alone and in conjunction with azathioprine (2.5 mg/kg). After one year, patients receiving prednisone and azathioprine had significantly lower doses of prednisolone than those receiving prednisolone alone. It should be noted that clinical outcomes with complete remission were similar in both groups.[8] In a similar study, no differences were noted in the mean total dose of prednisolone.[9] A systematic review and analysis showed that azathioprine had superior steroid-sparing effects compared to mycophenolate mofetil (MMF).[10] Although there is more evidence to support the use of azathioprine, MMF is more frequently used in PV due to its more favourable side effect profile and ease of use.

Mycophenolate Mofetil

MMF depletes guanosine nucleotides in T and B lymphocytes and inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation. MMF is used at a dose of 2–3 g/day in PV. The gastrointestinal side effects of MMF may be overcome with the use of enteric-coated mycophenolate sodium. MMF has a similar action to azathioprine, but with less myelosuppression but more gastrointestinal side effects.

The findings from studies on the steroid-sparing effects of MMF in PV have been conflicting. Two randomized trials found a statistically significant reduction in steroid use in patients who received MMF, while one randomized trial failed to show this.[11] A network meta-analysis of randomized trials also did not show a steroid-sparing effect.[7] A meta-analysis compared azathioprine and MMF and confirmed that MMF was inferior in its steroid-sparing effect.[10] Drug adverse effect profiles, comfort, and familiarity of clinicians generally guide selection between these two drugs.

Recalcitrant and Emerging Therapies

Refractory cases of PV require escalation of management with therapies such as intravenous immunoglobulin (IVIG), immunoadsorption, plasmapheresis, and cyclophosphamide. These therapies are usually added to a baseline immunosuppression regimen that includes steroids plus conventional immunosuppressants. However, due to the high costs, availability, and the technical difficulty associated with administering IVIG, plasmapheresis, and immunoadsorption, these treatments are limited to refractory cases only. Cyclophosphamide is considered as a rescue drug and is reserved for recalcitrant cases due to its unfavourable side effect profile, which includes cytopenia, sterility, and bladder cancer. Numerous new emerging therapies are currently being studied for PV (**Table 2**).[12]

IVIG

IVIG, a blood product that is comprised of pooled plasma, is used for its immunomodulatory effects in several inflammatory conditions. Its mechanism of action involves the degradation of immunoglobulins by binding to the neonatal Fc Receptor (FcRn). Considering that IVIG is not immunosuppressive, it can be administered in combination with systemic steroids and other immunosuppressants in cases of recalcitrant PV.[13] Due to its rapid onset of action, IVIG can be administered prior to assessing the response to rituximab in severe cases. A multi-centre randomized, placebo-controlled, double-blind study showed that administering IVIG at 2 g/kg over 5 consecutive days every 4 weeks is a safe and effective treatment option in steroid-resistant PV.[14] Side effects of IVIG include headache, nausea, fevers, tachycardia, aseptic meningitis, acute renal failure, and thromboembolic events. Aseptic meningitis is a serious side effect that requires immediate termination of treatment. The

Target	Category	Approved	Under Trial	Candidates
B-cell	CD20 mAb (First generation)	Rituximab		
	CD20 mAb (Second generation)			veltuzumab ocrelizumab
	CD20 mAb (Third generation)		ofatumumab	obinutuzumab ocaratuzumab
	CD19 mAb			inebilizumab
	BTK inhibitor	Rilzabrutinib[δ]	tirabrutinib	ibrutinib
Dsg3-specific B cells			CAAR-T cell	
T cell and T cell-B-cell interaction	CD25			daclizumab
	PolyTregs		NCT03239470	
Autoimmune cells				Autologous hematopoietic stem cell
Cytokines	TNF-α			etanercept infliximab
	IL-6			tocilizumab
	IL-4			dupilumab
	BAFF		VAY736	atacicept
Other	Fas ligand			PC111
	FcRn	SYNT001[δ]	efgartigimod	

Table 2. Emerging therapeutic agents and their status of clinical trial for pemphigus vulgaris; *adapted from Yuan 2022*.

Abbreviations: BAFF: B-cell-activating factor of the tumour-necrosis-factor family, **BTK:** Bruton tyrosine kinase, **CAAR:** chimeric autoantibody receptor, **Dsg-3:** Desmoglein 3, **FcRn:** neonatal Fc Receptor, **IL:** interleukin, **mAB:** monoclonal antibody

δ Granted Orphan Drug Designation by the United States FDA for PV therapy

absence (not deficiency) of serum IgA needs to be excluded prior to IVIG therapy, as this could lead to anaphylaxis.

Immunoadsorption/Plasmapheresis

Immunoadsorption removes circulating IgG autoantibodies, whereas plasmapheresis non-selectively removes plasma proteins from the circulation. The combination of immunoadsorption and immunosuppressive therapies is considered effective in treating severe PV as it is able to promptly remove the pathogenic autoantibodies.[15] The high cost, lack of availability in most countries, and potential side effects (venous thrombosis and infections) with immunoadsorption limit its use in treating PV. Plasmapheresis has limited efficacy in removing pathogenic autoantibodies and lacks high-quality trials showing its efficacy. As such, plasmapheresis is no longer a mainstay in the treatment of refractory PV.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T cell technology has revolutionized cancer therapy and is currently being studied for PV. In this method, T cells from a patient's own blood are genetically modified in the laboratory to express a CAR that is able to recognize a specific target antigen. Engineered chimeric Dsg-3 autoantibody receptor (CAAR) T cells have been created for PV and show an affinity for Dsg-3 B cells leading to their selective elimination.[16] Studies using mouse models have shown that these CAAR T cells improve clinical outcomes in PV and reduce pathogenic IgG antibodies.

Adjunct Therapies

Due to its chronic and relapsing course, it is important to consider prophylactic medications to prevent complications from treatment for PV. The American College of Rheumatology guidelines recommend taking vitamin D (600–800 IU daily) and calcium (1000–1200 mg once daily) supplements to prevent osteoporosis during long-term (≥3 months) steroid therapy.[17] Bisphosphonates such as alendronate or risedronate can be initiated in patients with risk factors (postmenopausal women, men aged >50 years, positive osteoporosis screening score), although some guidelines advocate routine use of bisphosphonates with prednisone >7.5 mg/d for ≥3 months.[3,18] There is insufficient evidence to routinely add proton pump inhibitors for gastric ulcer prevention while on steroids. Thus, the decision can be individualized for each patient depending on their risk factors (concurrent non-steroidal anti-inflammatory use, prior history of gastric ulcers, comorbidities).[3] Prophylaxis for pneumocystis pneumonia (PCP) is not routinely indicated for PV patients, despite prolonged use of immunosuppressive therapies.[19]

Vaccinations

Prior to starting any immunosuppressive medication, a patient's vaccine history should be obtained, and they should be advised to receive any necessary vaccinations. Live vaccinations are contraindicated for patients on high dose steroids (>20 mg/day) and immunosuppressive medications, and should be delayed until at least one month after discontinuation, depending on the medication and its half-life.[20] It is recommended that patients on oral steroids or immunosuppressive therapy receive non-live vaccines such as inactivated influenza, inactivated shingles, COVID-19, and pneumococcal vaccines. For pneumonia vaccination, it is recommended to administer pneumococcal conjugate (PCV13) followed by a dose of the pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later in patients on immunosuppressive medications. For vaccines given as a series (i.e. shingles vaccine, hepatitis B vaccine, etc.), the first dose should ideally be administered before starting therapy to ensure the best response. Other standard inactive vaccines (i.e. tetanus, diphtheria, pertussis, polio, among others) should also be up to date. Non-live vaccines should ideally be administered at a minimum 2 weeks prior to starting traditional immunosuppressive therapy (i.e. azathioprine, mycophenolate mofetil) to enhance vaccine immunogenicity. The administration of non-live vaccines should be delayed for a minimum of 2–4 weeks before starting rituximab.[21] Any additional or follow-up vaccines should be delayed until at least 6 months after rituximab therapy. Patients can receive non-live vaccines while on any immunosuppressant to acquire some immunity and can be revaccinated at a later time, especially if disease severity does not allow delays.

Conclusion

The objective of treating PV is to halt disease development and heal existing erosions. Rapid and effective treatment is critical for those with severe disease. Management of PV should be personalized for each patient depending on disease severity, age, comorbidities, and personal preferences. The use of systemic steroids and immunosuppressive agents has improved the prognosis of PV, however there can be significant morbidity associated with complications of this treatment. Larger randomized clinical trials are necessary to evaluate the efficacy of treatment agents in PV.

Correspondence

Bahar Bahrani, MD, FRCPC
Email: bbahrani@providencehealth.bc.ca

Financial Disclosures

None declared.

References

1. Murrell DF, Peña S, Joly P, Marinovic B, Hashimoto T, Diaz LA, et al. Diagnosis and management of pemphigus: recommendations of an international panel of experts. J Am Acad Dermatol. 2020;82(3):575-585. e1. doi:10.1016/j.jaad.2018.02.021.
2. Harman KE, Albert S, Black MM; British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. Br J Dermatol. 2003;149(5):926-937. doi:10.1111/j.1365-2133.2003.05665.x.
3. Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European academy of dermatology and venereology (EADV). J Eur Acad Dermatol Venereol. 2020;34(9):1900-1913. doi:10.1111/jdv.16752.
4. Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori Let al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. J Am Acad Dermatol. 2008;58(6):1043-1046. doi:10.1016/j.jaad.2008.01.012.
5. Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. Lancet. 2017;389(10083):2031-2040. doi:10.1016/S0140-6736(17)30070-3.
6. Werth VP, Joly P, Mimouni D, Maverakis E, Caux F, Lehane P, et al. Rituximab versus mycophenolate mofetil in patients with pemphigus vulgaris. N Engl J Med. 2021;384(24):2295-2305. doi:10.1056/NEJMoa2028564.
7. Lee MS, Yeh YC, Tu YK, Chan TC. Network meta-analysis-based comparison of first-line steroid-sparing adjuvants in the treatment of pemphigus vulgaris and pemphigus foliaceus. J Am Acad Dermatol. 2021;85(1):176-186. doi:10.1016/j.jaad.2020.08.028.
8. Chams-Davatchi C, Esmaili N, Daneshpazhooh M, Valikhani M, Balighi K, Hallaji Z, et al. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. J Am Acad Dermatol. 2007;57(4):622-628. doi: 10.1016/j.jaad.2007.05.024.
9. Chams-Davatchi C, Mortazavizadeh A, Daneshpazhooh M, Davatchi F, Balighi K, Esmaili N, et al. Randomized double blind trial of prednisolone and azathioprine, vs. prednisolone and placebo, in the treatment of pemphigus vulgaris. J Eur Acad Dermatol Venereol. 2013;27(10):1285-1292. doi:10.1111/j.1468-3083.2012.04717.x.
10. Martin LK, Werth VP, Villaneuva EV, Murrell DF. A systematic review of randomized controlled trials for pemphigus vulgaris and pemphigus foliaceus. J Am Acad Dermatol. 2011;64(5):903-908. doi:10.1016/j.jaad.2010.04.039.
11. Ioannides D, Apalla Z, Lazaridou E, Rigopoulos D. Evaluation of mycophenolate mofetil as a steroid-sparing agent in pemphigus: a randomized, prospective study. J Eur Acad Dermatol Venereol. 2012;26(7):855-860. doi:10.1111/j.1468-3083.2011.04170.x.
12. Yuan H, Pan M, Chen H, Mao X. Immunotherapy for pemphigus: present and future. Front Med (Lausanne). 2022;9:901239. doi:10.3389/fmed.2022.901239.
13. Amagai M, Ikeda S, Shimizu H, Iizuka H, Hanada K, Aiba S, et al. A randomized double- blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol. 2009;60(4):595-603. doi:10.1016/j.jaad.2008.09.052.
14. Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Esmaili N, Balighi K, Hallaji Z, et al. Pemphigus: analysis of 1209 cases. Int J Dermatol. 2005;44(6):470-476. doi:10.1111/j.1365-4632.2004.02501.x.
15. Didona D, Maglie R, Eming R, Hertl M. Pemphigus: current and future therapeutic strategies. Front Immunol. 2019;10:1418. doi:10.3389/fimmu.2019.01418.
16. Ellebrecht CT, Bhoj VG, Nace A, Choi EJ, Mao X, Cho MJ, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. Science. 2016;353(6295):179-184. doi:10.1126/science.aaf6756 .
17. Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, et al. 2017 American College of Rheumatology Guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol. 2017;69(8):1521–1537. doi:10.1002/art.40137.
18. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid induced osteoporosis. Arthritis Care Res (Hoboken). 2010;62(11):1515-1526. doi:10.1002/acr.20295
19. Lehman JS, Kalaaji AN. Role of primary prophylaxis for pneumocystis pneumonia in patients treated with systemic corticosteroids or other immunosuppressive agents for immune-mediated dermatologic conditions. J. Am. Acad. Dermatol. 2010;63(5):815-823. doi:10.1016/j.jaad.2009.11.588.
20. National Center for Immunization and Respiratory Diseases. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(2):1–64
21. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66(7):1016–1026. doi:10.1002/acr.22246.