Updates on the Management of Autoimmune Bullous Diseases

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Abstract

Background: Autoimmune bullous diseases are associated with high morbidity and mortality. Traditionally, systemic corticosteroids and conventional immunosuppressive agents have been the mainstay of treatment, but their broad immunosuppressive effects and long-term complications have prompted the exploration of newer more targeted therapies. **Materials and Methods:** This review explores the evolving landscape of therapeutic options for immunobullous diseases, with a particular focus on pemphigus, bullous pemphigoid (BP), and mucous membrane pemphigoid, by searching PubMed, clinicaltrials.gov, and Cochrane databases for published literature from 2014 to 2023. **Results / Discussion:** We discuss emerging treatments for pemphigus such as B cell modulatory drugs, anti-inflammatory drugs, those inhibiting autoantibody half-life or blister-inducing activity, and stem cell therapy, while offering insights into the level of evidence, potential benefits, and limitations of each approach. The role of biologics and novel therapies like rituximab, omalizumab, and dupilumab in reshaping the management of BP is also discussed. **Conclusion:** The article highlights the need for further research, clinical trials, and comparative studies to determine the most effective and safest treatment options for patients with immunobullous diseases.

Keywords: *Autoimmune bullous diseases, pemphigoid, pemphigus, update*

Introduction

Systemic corticosteroids and other conventional immunosuppressive agents have long been the established therapeutic approach for immunobullous diseases. However, owing to their broad immunosuppressive effect, adverse effects on long-term use, and the necessity for prolonged administration, there is a need for targeted and safer treatment options. Most of the drugs for autoimmune bullous diseases (AIBDs) have been extrapolated from the treatment of rheumatological, hematological, or autoimmune diseases.

Literature Search Strategy

Based on this, PubMed, clinicaltrials.gov, and Cochrane databases were searched for published literature using the keywords "blistering disease", "pemphigus", and "pemphigoid". Articles published in the English language from 2014 to 2023, including meta-analyses, reviews, clinical studies, reports, and case series, were retrieved and read, and relevant cross-references were examined. Similarly, trials registered at clinicaltrials.gov were also collected. Of 500 articles screened after the title and abstract screening, 78 articles (4 guidelines, 18 trials, 16 reviews and meta-analysis, 40 case reports and case series) were read in detail. The pertinent data were assigned levels of evidence (LoE) as per the Oxford Centre for Evidence-Based Medicine LoE scheme.[1]

In this narrative review, we discuss newer emerging therapeutic options for AIBDs, with a focus on pemphigus, bullous pemphigoid (BP), and mucous membrane pemphigoid (MMP).

Updates on the Management of Pemphigus

The introduction of rituximab has resulted in a significant transformation in the therapeutic landscape of AIBDs, notably in the context of pemphigus. It is now Food and Drug Administration (FDA) approved for treating moderate-to-severe pemphigus vulgaris (PV) in adults.[2] Nonetheless, an unmet need remains for therapeutic alternatives that can offer a more precise immunosuppressive action with a better safety profile. There is also a need for drugs

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that can expedite and prolong periods of remission or even demonstrate a curative potential.

In this review article, we have classified various treatments based on their site of action [Figure 1] in the treatment of pemphigus [Table 1].

Modulation of B cell function

The CD20 molecule serves as a membrane protein on the B-lymphocyte surface, encompassing early B cells, including pre-B cells, immature B cells, and mature B cells. It plays a critical role in the growth and differentiation of B cells. As CD20 molecules are not expressed on pro-B cells and plasma cells, the number of circulating B cells in the body can still be replenished through maturation despite prior treatment with anti-CD20 monoclonal antibodies.[3] These pro-B cells and plasma cells may play a role in the relapse of disease after anti-CD20 antibody treatments.[3]

Monoclonal anti-CD20 antibodies

Anti-CD20 antibodies can be classified into two distinct types based on their mechanism of action and binding site characteristics. Type 1 monoclonal antibodies, including rituximab, ofatumumab, veltuzumab, and ocrelizumab, predominantly induce a complement-dependent cytotoxic effect.[4] Conversely, Type II antibodies such as tositumomab or obinutuzumab elicit direct cell death and antibody-mediated cytotoxicity, with minimal influence from complement activation [Table 1].[4] Recent advancements in the understanding of immunology have suggested a novel mechanism known as 'tragocytosis' for the functioning of type 1 monoclonal antibodies.[5] This mechanism involves macrophages eliminating monoclonal antibody-CD20 complexes through the transfer of plasma membrane constituents. Consequently, this process precipitates the initiation of cell death.

A recent randomized controlled trial showed that low-dose rituximab (500 mg two doses, 15 days apart) has comparable efficacy as rheumatoid arthritis (RA) protocol in achieving disease remission (time to achieve clinical remission was 27.1 ± 1.6 weeks with low-dose rituximab and 26 ± 1.2 weeks with RA protocol, $P = 0.09$). However, immunological relapse was higher in low-dose rituximab patients (91% vs. 77%), but time to immunological relapse was similar. The authors showed that clinical relapse could be predicted by CD19+ B cell repopulation and prevented by giving an ultralow dose of rituximab (200 mg). This protocol was 37% more cost-effective than conventional treatment.[6] However, the study had a small sample size of 23 patients and may have been underpowered to detect a true difference between the two groups.

A study in healthy volunteers has shown a 95% reduction in B cell count for 3 months with a single dose of 100 mg

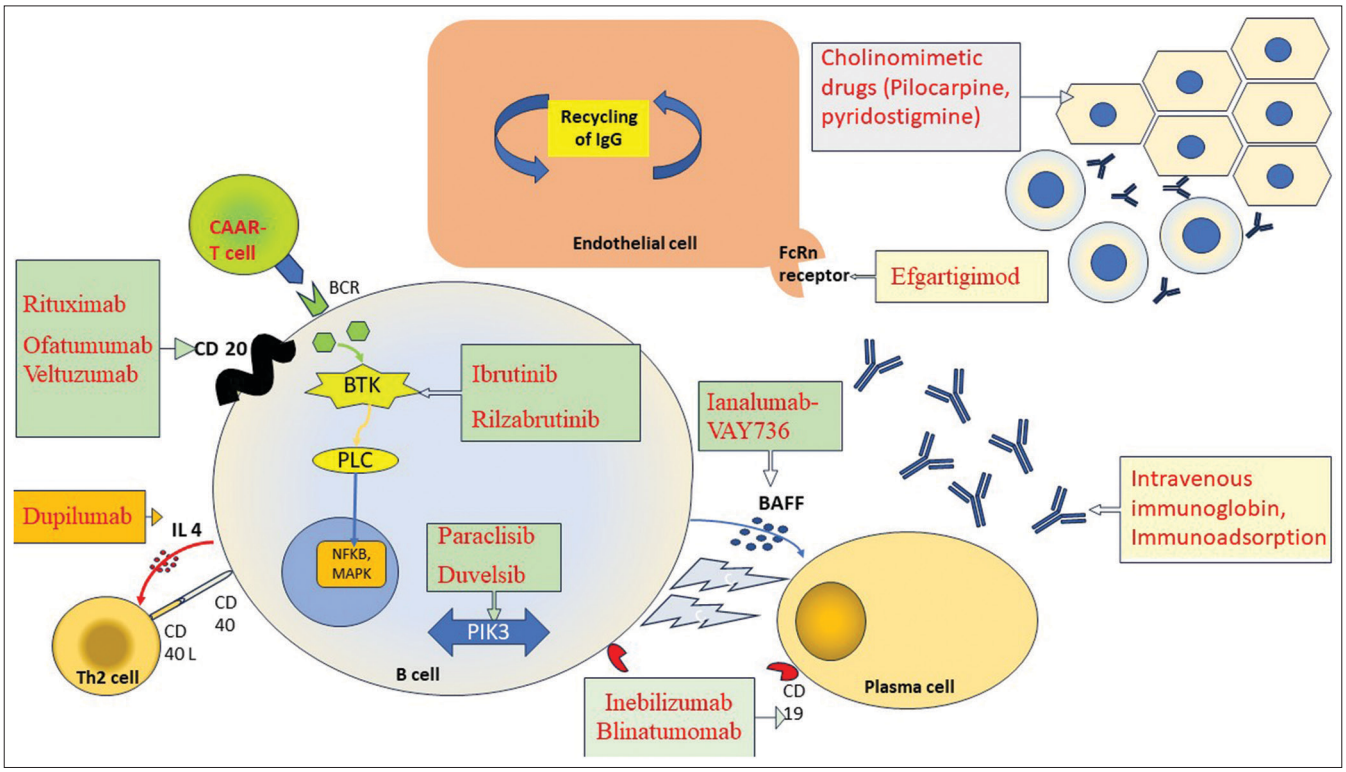

Figure 1: Schematic diagram representing drugs/therapies acting at various stages of pathogenesis in pemphigus. Key drugs acting at B cell or plasma cell level are anti-CD 20, anti-CD 19 monoclonal antibodies, CAAR-T cells, Bruton's tyrosine kinase (BTK) inhibitors, B-cell activating factor (BAAF) inhibitors (Light green box); drugs/therapies leading to reduction of half-life of IgG are FcRn antagonists, IVIg, immunoadsorption (light yellow box); drugs acting at level of acantholysis are cholinomimetic drugs (gray box); and drugs inhibiting various interleukins are IL-4 inhibitors (dark yellow box). BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; PLC: Phospholipase C; NFκB: Nuclear factor kappa B; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol-3 kinase

rituximab.[7] Encouraged by these promising findings in healthy subjects, ultralow-dose rituximab has been explored in pemphigus patients. A retrospective series of eight patients with baseline Pemphigus Disease Area Index (PDAI) ranging

Table 1: Emerging therapies in the treatment of pemphigus

Class of drug	Proposed mechanism of action	Drugs	Level of evidence	Current status
Drugs modulating B cell function				
Anti-CD20 antibodies	Antibody- dependent and complement-dependent lysis of B cells	Rituximab,	Level 1	Most effective steroid-sparing agent. Recommended as first-line agent in moderate-to-severe pemphigus[29]
		Ofatumumab	Level 4	Found effective in case reports; phase 3 trial terminated prematurely[11,12]
		Veltuzumab, Obinutuzumab	Level 4	Found effective in case reports of paraneoplastic pemphigus[10,13]
		Ocrelizumab, Tositumomab	Level 5	Not tried yet in pemphigus
Anti-CD19 antibodies	Killing of long-lived plasmablasts producing anti-Dsg IgG autoantibodies	Inebilizumab, Blinatumomab	Level 5	Not yet tried in pemphigus
B-cell activating factor (BAFF) inhibitor	BAFF inhibition leading to the elimination of autoreactive B cells and reduced longevity of plasma cells	Ianalumab-VAY736	Level 5	Phase 2 clinical trial in PV was prematurely terminated[17]
Bruton kinase (BTK) inhibitors	BTK inhibition leading to reduced antibody production and thereby inflammatory cytokines	Ibrutinib	Level 4	Found effective in case reports of paraneoplastic pemphigus[20]
		Rilzabrutinib	Level 2	Phase 3 trial showed no significant difference from placebo[22]
CAR-T (Chimeric Antigen Receptor- T cell) therapy	CAR-T therapy selectively targets pathological B cells and memory cells	Dsg3-CAR-T	Level 5	Phase 1 clinical trial undergoing[25]
Phosphatidylinositol-3 kinase (PI3K) inhibitor	PI3K∂inhibition leading to reduced activation and survival of B cells	Paraclisib	Level 5	Phase 2 trial in pemphigus was discontinued without disclosing results due to lack of interest from participants.[27]
		Duvelsib	Level 5	Not tried in pemphigus
Modulation of autoantibody (IgG) half-life				
FcRn antagonist	Block the binding of IgG to FcRn, thereby accelerating their breakdown and inducing a reduction in overall plasma IgG levels	Efgartigimod	Level 4	Demonstrated an early effect on disease activity and outcome parametersin phase 2 trial. Phase 3 trial undergoing.[27]
Immunoadsorption	Removes pathological antibodies		Level 2	Randomized controlled trial did not show the added advantage of immunoadsorption with the best medical treatment.[31]
Inhibition of inflammatory cytokines				
IL4 inhibitor	Reducing T helper 2 cytokine response leading to reduced production of antidesmoglein antibody	Dupilumab	Level 4	Found effective in case reports of pemphigus.[36]
TNF alfa inhibitor	Decreased ST18 (a transcription factor) expression in the skin of pemphigus by blocking TNF alfa	Etanercept	Level 4	Heterogenous results in case report and case series of pemphigus.[37]
IL 17 blockage		Secukinumab	Level 4	Efficacy shown in patients with pemphigus foliaceus.[37]
		Brodalumab, and Ixekizumab	Level 5	
mTOR pathway inhibitor	Improvement of Th2 cell differentiation and Treg cell differentiation	Rapamycin/ sirolimus	Level 4	Efficacy is shown in a case report. Clinical trial for its efficacy in pemphigus was prematurely terminated.[37]

Contd...

Table 1: Contd...

Class of drug	Proposed mechanism of action	Drugs	Level of evidence	Current status
Inhibition of blister-forming activity				
Cholinomimetic drugs	Increase expression of desmosomes by reducing its phosphorylation	Pilocarpine (topical)	Level 2b	Better reepithelization seen in placebo controlled trial.[41]
		Pyridostigmine (oral)	Level 4	Shown promising result in open-label study.[39]
Other treatment options				
Stem cell therapy	Depletion of autoreactive cells and repopulation of self-tolerant cells		Level 4	Shown promising result in open-label study.[42]
Polyclonal regulatory T cells (Poly Tregs)	Restore the lost immune tolerance against desmoglein		Level 5	Phase 1 trial undergoing in pemphigus vulgaris and foliaceus.[26]

from 4 to 20 treated with two doses of 200 mg rituximab showed a reduction in PDAI in six patients at six months, with a relapse rate of 25% in one year.[8] Another case series of eight PV patients treated with a single dose of 200 mg rituximab reported complete remission in five patients and partial remission in three patients.[9] The mean time to disease control was 7.5 weeks, with one relapse noted during the follow-up period ranging from 18 to 101 weeks. These reports suggest that ultralow-dose rituximab can become a potential therapy for patients with milder disease. Larger controlled trials with multiple dosing arms are required to find an optimal dose of rituximab for pemphigus.

In contrast to rituximab which is chimeric in nature, the more contemporary anti-CD20 molecules are characterized as humanized antibodies, thereby reducing their immunogenic potential and the likelihood of provoking transfusion reactions.[10]

Newer anti-CD20 antibodies, namely veltuzumab, obinutuzumab, and ofatumumab, have been tried in a few cases of pemphigus. Notably, veltuzumab and ofatumumab have been administered in isolated instances of rituximab-resistant PV, yielding favorable responses devoid of significant adverse effects.[10,11]

Ofatumumab, a fully human monoclonal antibody, was used at a dose of 300 mg on day 1, 1000 mg on day 8, and then 1000 mg every 28 days for 8 cycles. In these reports, clinical symptoms of pemphigus started improving after the second dose, and remission was achieved after one month of the ninth infusion.[11] Furthermore, a phase 3 clinical trial focusing on ofatumumab in PV was initiated; however, the trial was prematurely terminated with undisclosed outcomes due to a change in the drug sponsor.[12]

Veltuzumab has been used in a patient achieving partial remission with rituximab. After two doses of 325 mg veltuzumab subcutaneously at two-week interval, the patient achieved complete remission for two years.[10]

Obinutuzumab has shown promising results in a patient with follicular lymphoma accompanied by paraneoplastic pemphigus (PNP).[13] Significant improvement was observed both in lymphoma and the concurrent PNP. Future studies are required to compare the efficacy and safety profiles of these newer anti-CD20 monoclonal antibodies against the established benchmark, rituximab.

Anti-CD19 monoclonal antibodies

Inebilizumab and blinatumomab are antibodies that may affect both memory B-cells and plasma cells.[14] Unlike rituximab, which targets CD20, these monoclonal antibodies target CD19, which is present in both memory B cells and plasma cells. It is postulated that due to targeting of these cells, these drugs might lead to very long remissions or even cure of pemphigus.

Epratuzumab enhances the inhibitory signal from CD22 without depleting B-cells. Epratuzumab reduces CD19, 21, and 79b on B-cells and transfers them to NK-cells and T-cells. These drugs have been tested in lupus erythematosus with varying results and might be used for pemphigus in the future.[14]

B-cell activating factor (BAFF) inhibitors

BAFF and a proliferation-inducing ligand (APRIL), important members of the TNF-α family, have also been implicated in the pathogenesis of pemphigus. BAFF, also known as B-lymphocyte stimulator, is required for survival of B cells, elimination of autoreactive B cells, and longevity of plasma cells [Figure 1]. Recently, Daneshvar *et al.*[15] have demonstrated increased baseline BAAF levels in pemphigus patients compared to controls, and a gradual increase in BAFF levels at 3 and 6 months following rituximab infusion. It has been postulated that BAFF may be responsible for the reactivation of B cells in pemphigus, and anti-BAFF therapy can be used to prolong remission.

In Sjogren syndrome, anti-BAFF monoclonal antibody (Ianalumab-VAY736) has shown clinical improvement in disease scores.[16] Common adverse effects noted in this trial were nasopharyngitis and infusion reaction. A phase 2 clinical trial was initiated to determine the clinical effects of VAY736 in PV, but it was prematurely terminated in 2021.[17] According to data from trial registry updates, PDAI scores after 12 weeks were 5.9 for the

Table 2: Emerging therapies for the treatment of bullous pemphigoid

Class of drug	Proposed mechanism of action	Drugs	Level of evidence	
Anti-CD20 antibodies	Antibody-dependent and complement-dependent lysis of B cells	Rituximab	Level 4	Multiple case reports and series have shown improvement in bullous pemphigoid. No controlled studies are available.[43]
Anti-IgE antibodies	Inhibition of IgE binding to Fcε receptor leading to reduced activation of Th2 inflammation	Omalizumab	Level 4	Multiple case reports and series have shown improvement in bullous pemphigoid.[43]
		Ligelizumab	Level 4	Failed to reach primary endpoint in phase 2 clinical trial.[47]
Anti-IL4 antibodies	Downregulation of B-cell proliferation, eosinophil chemotaxis, and Th2-associated chemokine activity	Dupilumab	Level 4	Case reports and series have shown improvement in bullous pemphigoid.[43]
Complement system inhibitors Anti-C5aR1 monoclonal antibody	Inhibition of complement or its components leading to reduced granulocyte migration and inflammation	Avdoralimab	Level 4	Phase 2 open-label controlled trial has been started.[59]
		Nomacopan		Showed improvement in phase 2 controlled trial. Phase 3 trial has been started.[59]
Inhibitor of C5 and LTB4			Level 3	
IgG4 monoclonal antibody that targets the C1s component		Sutimlimab	Level 4	Larger phase 1 study is being undertaken. It has received FDA orphan drug status in the treatment of bullous pemphigoid.[59]
IL-5 Inhibitors	Inhibition of recruitment and activation of eosinophils	Reslizumab	Level 4	Excellent improvement in a case report.[49]
		Mepolizumab	Level 2	Failed to achieve primary endpoint in a randomized double-blind trial.[48]
		Benralizumab	Level 4	Being investigated in a double-blind phase 3 trial.[50]
IL-17 and IL-23 Inhibitors	Reduction in secretion of MMP-9 and neutrophil elastase	Secukinumab	Level 4	Demonstrated improvement in a case report.[53]
		Ixekizumab	Level 4	Failed to achieve primary endpoint in phase 2 study.[55]
		Ustekinumab	Level 4	Phase 2 open-label study is being undertaken.[56]
		Tildrakizumab	Level 4	Phase 1 study is being undertaken.[57]
Eotaxin-1 inhibition	Inhibition of eotaxin-1 leading to reduced eosinophil migration to the skin	Bertilimumab	Level 3	Phase 2 open-label study showed promising results. Results of double-blind controlled trial are awaited.[51]

group receiving 3 mg/kg of VAY736, 10.15 for the group receiving 10 mg/kg of VAY736, and 22.07 for the group receiving placebo, while Autoimmune Bullous Skin Disorder Intensity Scores (ABSIS) after 12 weeks for 3 mg/kg VAY736 group, 10 mg/kg VAY736 group, and placebo group were 2.19, 5.55, and 16.17, respectively, which were lower compared to their initial scores of 13.26, 16.38, and 33.75.[17] Currently, there are no published preliminary findings from this trial. Nonetheless, BAFF inhibitors could have potential benefits in treating pemphigus.

Bruton tyrosine kinase (BTK) inhibitors

BTK, a member of Tec family of kinase, is expressed by all B lymphocytes (from pre-B-lymphocytes to mature B lymphocytes) and plasma cells.[18] It is an important signaling molecule required for the activation of B-cell receptors. Inhibition of activation of B cells by BTK inhibitors leads to reduced production of antibodies and inflammatory cytokines [Figure 1]. Ibrutinib, an irreversible BTK inhibitor, is being used in the treatment of chronic lymphocytic leukemia (CLL), graft versus host disease, and RA.[19] The use of BTK inhibitor in pemphigus was first reported when ibrutinib led to improvement in PNP occurring in association with CLL.[20] Rilzabrutinib (PRN1008), an orally administered reversible covalent BTK inhibitor, has a better safety profile compared to the irreversible BTK inhibitors.[21] It does not lead to B-cell depletion or cytotoxicity or cause prolonged immunosuppression like

the anti-CD20 antibodies. Additionally, rilzabrutinib rapidly inhibits antibody-mediated immune cell activation through Fc-receptor signaling.[21]

In a single-arm, multicenter phase 2 trial, rilzabrutinib was investigated in 27 patients affected by PV, encompassing 9 newly diagnosed cases and 18 instances of relapse (comprising 11 with moderate disease and 16 with moderate-to-severe disease).[21] Notably, 52% of patients demonstrated disease control at none or minimal doses of corticosteroid at 4 weeks, with a good safety profile. Gastrointestinal discomfort including nausea, vomiting, and throat irritation were the frequent adverse effects, whereas only one participant encountered a grade 3 adverse event, namely cellulitis.[21] After this phase 2 trial, it received 'orphan drug' designation by food and drug administration (FDA) for the treatment of PV. Subsequently, a phase 3 clinical trial of rilzabrutinib (termed PEGASUS) was conducted; however, the outcomes of this trial were disheartening, displaying parallel rates of remission between the drug and placebo arms.[22] Hence, at present, there is mixed evidence regarding the effect of this group of drugs on PV management.

Chimeric antibody receptor (CAR)-T therapy

CAR-T cell therapy appears to be a promising and emerging therapeutic approach for both cancers and autoimmune disorders. CAR is an antigen receptor that guides T cells to target antigen-expressing cells independent of major histocompatibility complex interactions. CAR-T cells targeting CD19 have demonstrated excellent efficacy in achieving sustained remission in patients with B-cell malignancies.[23]

In PV, the pathogenic B cells express anti-Dsg3 receptors. The scientific rationale behind this therapy is based on designing the extracellular domain of a chimeric immunoreceptor to be Dsg3. It will confer cytotoxicity selectively to B cells possessing anti-Dsg3 B-cell receptors, thereby offering a targeted therapeutic approach for PV without causing global immunosuppression. In addition, it will eliminate memory B cells responsible for relapse, leading to a possibility of curing PV. In this technique, CAR constructs are inserted into isolated and activated T cells of the patient. Following the *in vitro* expansion of these cells, they are reintroduced into the patient's body, leading to the targeted elimination of specific cells.

In the mouse model, dsg3-CAR-T cells were long lasting, which suggests that these cells can induce long-lasting remission or even cure pemphigus.[24] Due to a limited number of target cells in PV, the theoretical risk of adverse effects such as cytokine release and tumor lysis syndrome is also anticipated to be lower than that observed in cancer treatments. The limitations include high cost and treatment failure in patients with multiple pathogenic antibodies besides anti-desmoglein 3 antibodies.

Tisagenlecleucel, a CD19-directed autologous T-cell immunotherapy, has been approved by FDA for the treatment of adult patients with relapsed or refractory follicular lymphoma, failing two or more lines of therapy.[23] Phase 1 trial of Dsg3-CAR-T is undergoing treatment of mucosal PV and is expected to be completed in 2026.[25]

Modulation of autoantibody (IgG) half-Life

FcRnantagonist

Fc receptor, a cell surface molecule of Fc part of immunoglobulin, is expressed by effector and memory B cells. FcRn (neonatal Fc receptor) plays a key role in the protection of IgG from degradation and antigen presentation to immune cells.[26] It provides short-term humoral immunity among neonates by recycling IgG antibodies received during the intrauterine period. In adult individuals, FcRn is prominently expressed in muscular tissues, vascular endothelial cells, and skin. FcRn-bound IgG is internalized via pinocytosis within acidic lysosomes, and subsequently released back into circulation after recycling.[26] This mechanism plays an important role in prolonging the half-life of IgG antibodies, where recycling outpaces new IgG production by approximately 40%. Thus, FcRn assumes a vital role in sustaining serum IgG levels.

Monoclonal antibodies antagonizing FcRn like efgartigimod (recently approved by FDA for myasthenia gravis) and syntimmune interact with FcRn receptors, leading to a reduction in circulating IgG antibody levels within serum while leaving other immunoglobulin classes unaffected [Figure 1].[26] This reduction in autoantibodies in circulation can potentially reduce downstream inflammatory cytokine activity. Furthermore, these monoclonal antibodies exert additional effects by obstructing FcRn-mediated antigen presentation to IgG, thereby possibly hindering the activation of T and B lymphocytes.

In contrast to conventional drugs such as rituximab and corticosteroids which primarily act at the level of B cells, FcRn antagonists function at the downstream targets and might lead to early clinical response and also reduce cumulative corticosteroid dosages.[26] Nevertheless, these therapies have drawbacks similar to current modalities, including nonspecific immunosuppression, parenteral mode of administration, risk of infection, and lack of sustained clinical improvement. In contrast to intravenous immunoglobulin (IVIg), which also acts at the antibody level, anti-FcRn monoclonal antibodies lack the ability to provide various immunomodulatory effects. Moreover, these agents will not be suitable for patients with concurrent infections.

Although these agents may cause rapid clearance of pathogenic antibodies, their effect on other aspects of autoimmunity (e.g., T and B cells, plasma cells, inflammatory cytokines), along with clinical effects on disease including remission duration, adverse effects, and

the emergence of anti-drug antibodies will likely determine their application in the treatment of pemphigus.

Two FcRn receptor antagonists are being tried in pemphigus-efgartigimod (ARGX-113) and ALXN1830(SYNT001). An open-label phase 2 clinical trial (NCT03334058) evaluated the effectiveness of efgartigimod in mild to moderate PV and PF.[27] This trial involved 34 participants who received efgartigimod at dosages of 10 or 25 mg/kg intravenously, either as a stand alone treatment or in combination with low-dose oral prednisone. Disease control was achieved in 90% of patients within a median of 17 days and continued treatment with efgartigimod along with a median prednisone dose of 0.26 mg/kg/day led to complete clinical remission in 64% of patients within 2 to 41 weeks. Significant reduction in serum total IgG and anti-desmoglein autoantibodies was observed that correlated with a reduction in PDAI scores. Most adverse events were mild, reported by 84% of those receiving 10 mg/kg and 87% of those receiving 25 mg/kg, while serious adverse events were encountered in two patients (pneumonia and tibia fracture) at 10mg/kg dose, which were probably unrelated to the drug. These findings highlight the potential of efgartigimod in achieving early disease control and complete remission in pemphigus, besides corticosteroid-sparing action. Based on these promising results, a phase 3 randomized controlled trial is currently underway (NCT04598451) to further investigate its efficacy and safety in PV and PF.

ALXN1830 (SYNT001) is a humanized IgG4 monoclonal antibody that targets FcRn to interrupt its interaction with IgG. An open-label phase 1B/2 clinical trial (NCT03075904) was conducted to assess its safety and dosing in PV or PF patients.[28] Eight participants received five doses of ALXN1830 at 10 mg/kg over five weeks, with follow-up till day 112.[28] All eight patients experienced at least one minor adverse effect, with headache being the most common (46%) and one patient encountered two serious adverse effects, i.e., cutaneous herpes simplex infection and methicillin-resistant *Staphylococcus aureus* infection. There was a median decrease in total IgG levels by 32.5% on day 5, and 57.6% on day 30, with a return to around 25% of baseline levels by the end of the study (day 112). PDAI decreased in six patients, with a median reduction to 39.6% of the baseline value. Five patients showed improvement on day 28 and the sixth patient on day 84.[28] Anti-dsg1 and 3 titers were reduced in four of the six responding patients. In contrast, patients with worsening clinical symptoms showed elevated anti-dsg1 levels but without significant change in anti-dsg3 levels.This proof-of-concept study demonstrated clinically meaningful efficacy besides unacceptable safety and tolerability profile.

Immunoadsorption

Immunoadsorption removes pathological antibodies in pemphigus. Unlike plasmapheresis, it specifically targets IgGs and immune complexes, making it more efficient and safer. Initially, many case series have shown improvement in pemphigus without causing significant immunosuppression, especially in patients with multiple comorbidities. It has been recommended as a second- or third-line treatment and can be combined with immunosuppressive drugs.[29,30] It is well-tolerated and has shown limited adverse effects. However, its high cost and limited availability are drawbacks. Recently, a multicenter randomized controlled trial of 72 patients with PV and foliaceus comparing safety and efficacy profiles of best medical treatment [BMT group] (prednisolone 1.0 mg/kg/d plus azathioprine or mycophenolate) alone versus best medical treatment with immunoadsorption [BMT+IA group] has been prematurely terminated due to safety concerns. The primary endpoint (time to achieve complete remission on therapy) was not statistically different but the cumulative steroid dose was significantly less in the BMT+IA group (difference −1,214; 95%CI, −2,225 −70; $P = 0.03$).[31] Serious adverse effects were more in BMT+IA group though overall adverse effects were more in the BMT group. Studies on its effectiveness are contradicting and further studies are required to understand its indications, efficacy, and safety profile.[31]

Intravenous immunoglobins

IVIg, a concentrated form of human IgG derived from multiple donors, is used in treating various autoimmune disorders. Its exact mechanism is not fully understood but is thought to act via mechanisms like neutralizing pathogenic antibodies, suppressing antibody production, accelerating antibody catabolism, and modulating the immune system [Figure 1].[32] Before IVIg infusion, no investigation is required. Checking serum IgA level before treatment is debatable, as low IgA level may lead to antibody formation against it but most patients with these antibodies tolerate IVIg. Currently, available IVIg products have minimal IgA content, and screening for IgA deficiency can cause delay and limit treatment without clear benefits.[33]

In PV, IVIg is considered when other treatments are unsuitable and rapid control of the disease is required. Various protocols have been developed such as sequential therapy (i.e., rapid control of disease with IVIg followed by other steroid-sparing agent for maintenance), IVIg as the sole adjuvant, and combination therapy with other steroid-sparing immunosuppressants like rituximab. Ahmed and colleagues proposed a pemphigus treatment plan combining rituximab and IVIg.[34] The protocol involves 12 rituximab injections over 6–14 months with IVIg. Phase 1 includes initial immune-prophylaxis with IVIg, followed by weekly rituximab for 8 weeks. Phase 2 has monthly IVIg cycles till 15% B-cell repopulation. In phase 3, patients receive six additional IVIg cycles. The protocol aims to eliminate inflammation, restore immune balance, and achieve prolonged drug-free remission. While longer

and costlier, this approach has shown extended remissions in around 50 patients of various autoimmune blistering diseases without serious adverse effects.[32,34]

Inhibition of inflammatory cytokines

For several years, T helper 2 pathway-related cytokines such as interleukin (IL)-4 and IL-13 have been proposed in the pathogenesis of pemphigus [Figure 1].[35] Some studies have also demonstrated increased levels of IL-4 in pemphigus. Dupilumab, a fully human IgG4 monoclonal antibody, targets the IL-4RA protein. Its binding to IL-4 receptors obstructs the signaling of IL-4 and IL-13, thereby inhibiting the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway involved in inflammation. It has been approved for atopic dermatitis, asthma, chronic rhinosinusitis, and eosinophilic esophagitis. Few case reports have demonstrated its efficacy in PV.[36] However, present data are insufficient to conclude on the effectiveness of dupilumab in pemphigus, and further research is required to determine its efficacy.

Various other innovative approaches being explored include the investigation of IL-17 inhibition, tumour necrosis factor alfa (TNF-α) blockade, and mTOR pathway inhibition.[37] All these pathways are based on a theoretical understanding of the pathogenesis of pemphigus and isolated reports of improvement in patients in whom the drug was used to treat concomitant psoriasis. Although a clinical trial for evaluating the efficacy of sirolimus in pemphigus was started, it was prematurely terminated due to lack of funding.

Inhibition of blister-inducing activity

Cholinomimetic drugs

Desmosomes and adherence junctions play a critical role in the cell-to-cell adhesion of keratinocytes, and the acetylcholine axis increases their expression on the cell surface. Due to antibody formation against acetylcholine (anti-Ach) receptors in pemphigus, this axis is not maintained leading to phosphorylation of the desmosomes and weakening of intercellular adhesions. Although anti-AchR antibodies are not the primary culprit antibodies in pemphigus, they augment the effects of anti-desmosomal antibodies by reducing desmosomal expression on the cell surface. Some preclinical studies have suggested that cholinergic drugs can prevent acantholysis in subjects without anti-AchR antibodies by producing a positive effect in the acetylcholine axis and increasing the expression of desmosomes [Figure 1].[38]

Cholinomimetic drugs like oral pyridostigmine and topical pilocarpine have been tried in pemphigus. In a small open-label study published in 2004, eight patients (six PV, one PF, and one PNP) were treated with oral pyridostigmine alone or with low-dose corticosteroids. Complete and partial remission were observed in one patient each, improvement in two patients, and no improvement was observed in four patients.[39] Since then, there have been no studies testing oral pyridostigmine in pemphigus.

In a double-blind, placebo-controlled trial, 64 cutaneous lesions in 3 PV patients were treated with either pilocarpine 4% gel or placebo gel. After 15 days, the epithelization index of lesions treated with topical pilocarpine was significantly better than placebo (mean 40.3 vs. 24.4, $P < 0.001$).[40] In another open-label study, 20 PV patients having resistant oral erosions were given topical pilocarpine 2% drops twice daily for 180 days, along with continuation of systemic immunosuppression at the same dose throughout the study.[41] After 180 days, there was a significant reduction in the mean area of erosions.[41] Pre- and post-treatment levels of anti-desmoglein 1 and 3, and antiacetylcholine receptor antibodies, however, in both the serum and saliva were similar.

These preliminary studies suggest a potential adjuvant effect of topical cholinomimetic drugs in healing pemphigus erosions; however, this needs to be confirmed in larger studies.

Stem cell therapy

Stem cells are undifferentiated cells in various tissues with properties of self-renewal, differentiation, and plasticity. They reside in stem cell niche and help in homeostasis and tissue repair. Based on the source of these cells, they can be divided into embryonic, somatic, and induced pluripotent cells. In autoimmune diseases, hematopoietic stem cells (HSCs) have been used, which cause depletion of autoreactive cells and repopulation of self-tolerant cells. HSCs can be taken from self (autologous) or HLA-matched donor (allogenic). Stem cell therapy has been reported in recalcitrant pemphigus with both autologous and allogeneic stem cell transplantation from various centers (including a series of 11 patients from Ahmedabad, India).[42] Among all reported patients, 90–100% of patients achieved clinical remission on tapering the dose of steroid at 6 months, and around 75–100% of patients had drug-free remission at 5 years in various series.[42] Most common adverse effects were infections including sepsis, and one patient died among the 24 reported cases.[42] Major disadvantages of this treatment are its high cost, risk of infection, and complications of stem cell treatment such as graft versus host disease and Epstein Barr virus-associated lymphoproliferative disorders. As safer and cheaper alternatives like rituximab have become available, stem cell therapy has not gained much popularity in the management of pemphigus.

Updates in the Management of BP

BP, a subepidermal blistering disease that primarily targets BPAG 1 and 2, predominantly affects the elderly

population. At present, the therapeutic approach involves the utilization of immunosuppressive agents like potent topical steroids, oral corticosteroids, and anti-inflammatory medications like tetracyclines and nicotinamide. Due to the presence of multiple comorbidities among these patients, administration of oral corticosteroids and IVIG is often not preferred. Moreover, other anti-inflammatory agents exhibit limited efficacy in severe disease. Although no biological agents have been approved for the treatment of BP, based on the current understanding of pathogenesis, various biologic drugs have been repurposed for the management of recalcitrant disease. Newer drugs which have been tried in clinical practice are discussed in this review [Figure 2 and Table 2].

B cell depletion therapies

After the successful use of rituximab in pemphigus, it has also been tried in patients with moderate-to-severe BP. Although no controlled trials are available, in a systemic review of 122 patients, most of whom were resistant to conventional drugs, 70.5% patients had complete remission, 23.8% had partial remission, and 4.9% did not achieve remission after rituximab infusion.[43] In a mean follow-up period of 21.9 months, the average time to remission was 5.7 months, while 20.5% of patients noticed recurrence.[43] The most common adverse effects were infection (6.6%) followed by altered mental status (3.3%). Death occurred in 9% of patients.[41] Close monitoring is required for infection in these patients as older age, concomitant use of azathioprine, prednisolone >15 mg/day, renal disease, and diabetes mellitus are associated with increased risk of infection after rituximab infusion.[44] In recent S2K guidelines by the European Academy of Dermatology, rituximab has been included as third line management in difficult-to-treat BP.[45]

Biologics targeting type 2 immune response

T helper type 2 (Th2) response involving the secretion of IL-4, IL-5, and IL-13, inturn, leads to stimulation of type 2 immunity characterized by high IgE and eosinophilia. Various studies have demonstrated predominant Th2 responses in BP by showing a positive correlation of its severity with serum levels of anti-BP 180 IgE antibodies, linear IgE deposition at the dermo-epidermal junction, blood and tissue eosinophilia, and other Th2 cytokines [Figure 2].[46] Various biologicals and other drugs targeting Th2 response have, therefore, been tried, with varying success. The most studied drugs include omalizumab and dupilumab.

Omalizumab

Omalizumab is an anti-IgE monoclonal antibody initially approved for asthma in the early 2000s. It is now approved for chronic urticaria and nasal polyps.[46] The dosing regimen is 150 mg/300 mg subcutaneously every 4 weeks. Adverse reactions include rare cases of anaphylaxis (0.1–0.2% incidence) that can be delayed up to 2 h in the first 3 doses and up to 30 min in subsequent doses.[42] Minor reactions like injection site reaction, headache, and urticaria can also occur.

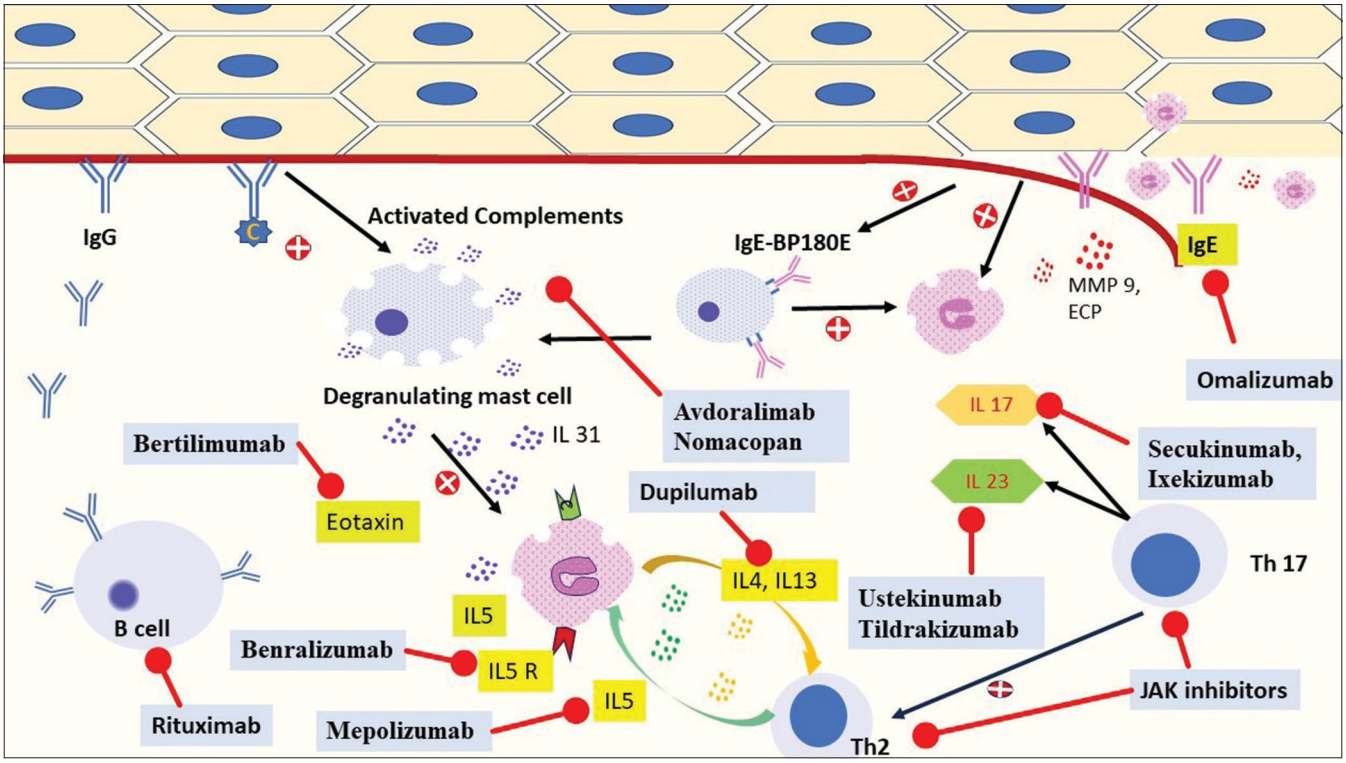

Figure 2: Schematic diagram of pathogenesis of bullous pemphigoid with sites of action of various drugs

A recent review reported complete remission in 68% of patients (36 out of 53) with omalizumab, similar to rituximab (70% of 122 patients).[43] Updated S2K guidelines recommend omalizumab in BP patients with urticarial plaques, high serum IgE levels, and associated neoplasia.[45] However, a study on 56 patients found no differences among responders (n = 31) versus nonresponders (n = 25) with respect to serum IgE levels (P = 0.84) or eosinophil count (P = 0.79).[46]

Omalizumab appears to be a promising drug for BP without causing significant immunosuppression. It can be an option in corticosteroid-dependent and relapsing BP cases in which other immunosuppressives are contraindicated. However, well-designed comparative trials are needed to ascertain the therapeutic status of this agent in BP.

Ligetizumab, a second-generation anti-IgE monoclonal antibody, has failed to reach the primary endpoint in a phase 2 clinical trial.[47]

Dupilumab

Dupilumab, a humanized monoclonal antibody targeting the α-subunit of IL-4 that leads to inhibition of IL-4 and IL-13 signal transduction [Figure 2], has been tried in BP. A review of 44 patients receiving dupilumab treatment showed complete remission in 66.7% and partial remission in 19.4% of patients within 4.5 months, with a recurrence rate of 5.6%.[43] Like omalizumab, it also does not cause significant immunosuppression. Its efficacy in large controlled trials needs to be ascertained.

Other drugs targeting type 2 immune response

In patients with eosinophilia, IL-5 and IL-17 act synergistically to increase the catalytic activity of eosinophils [Figure 2]. Hence, therapies targeting IL-5, IL-17, IL-23, eotaxin, or CCR3 have been tried in BP. IL-5 inhibitors have shown mixed results. Reslizumab has shown excellent improvement in a case report, but another IL-5 inhibitor, mepolizumab, has failed to achieve the primary endpoint in a randomized double-blind trial.[48,49] Another IL-5 antagonist benralizumab, targeting both eosinophils and basophils, is being investigated in a double-blind phase 3 trial.[50]

Eotaxin and CCR3 are responsible for the recruitment of eosinophils in BP lesions. Bertilimumab, a monoclonal antibody targeting eotaxin-1, has shown an 81% reduction in disease activity in an open-label phase 2 trial involving 12 patients.[51] AKST4290, an oral CCR3 inhibitor, has completed a double-blind placebo-controlled trial in mild-to-moderate BP, the results of which are not yet available.[52]

IL-17 inhibitors have also shown varying results in the treatment of BP. Secukinumab and ixekizumab showed improvement in two case reports, but ixekizumab failed to achieve the primary endpoint in an open-label phase 2 trial.[53-55] IL-23 inhibitors like ustekinumab and tildrakizumab are also being investigated in ongoing trials.[56,57]

Few case reports have shown improvement in BP with JAK inhibitors like baricitinib, upadacitinib, and tofacitinib.[58]

Complement system inhibitors

Complement activation is integral to the development of blisters in BP. Components like C1, C3, C3d, properdin, and C5 have been found at the dermo-epidermal junction and blister fluid. C5a induces inflammation and neutrophil recruitment facilitated by leucotriene B4 (LTB4). Nomacopan (inhibits C5 and LTB4), avdoralimab (anti-C5aR1 monoclonal antibody), and sutimlimab (anti-C1s complement monoclonal antibody) have been tried in BP [Figure 2]. These drugs have shown promising results in phase 1 trials and further trials have been started. FDA has designated 'orphan drug' status to sutimlimab in 2017.[59]

Updates in the Management of Mucous Membrane Pemphigoid

MMP is a subepidermal AIBD characterized by the predominant involvement of mucous membranes and associated scarring. As MMP has low incidence (1–2 per million per year), controlled trials of various therapies are lacking. The treatment guidelines of MMP are based on case series and expert opinion. Currently, conventional anti-inflammatory and immunosuppressive agents like dapsone, corticosteroids, azathioprine, cyclophosphamide, and IVIg are the mainstay of therapy.

Lee *et al*.[60] have reported remission in mild oral MMP patients with twice daily application of topical tacrolimus 0.1% ointment for two months.

Similar to other AIBDs, rituximab has also shown promising results in oral and ocular MMP. Data collected from various reports in 120 MMP patients treated with rituximab have shown that 68% of patients achieved complete remission and 13% achieved partial remission with rituximab.[61] In most cases, rituximab was combined with conventional immunosuppressive agents.[61]

Various other drugs like baricitinib (oral JAK inhibitor),[62] bortezomib (proteasome inhibitor),[63] and etanercept (TNF-α inhibitor)[64] have been reported effective in the management of refractory MMP in isolated case reports. Currently, an open-label phase 3 clinical trial is being conducted to compare the safety and efficacy of rituximab and cyclophosphamide in MMP. Similarly, a phase 2 trial is being undertaken to assess the efficacy of baricitinib in this disease.

Conclusion

As our understanding of AIBD pathogenesis continues to expand, novel therapeutic targets will emerge leading

to the development of more effective agents. A variety of targeted therapies are in the preliminary phases of testing. Most of these drugs have been repurposed from other autoimmune diseases and data of their efficacy in AIBDs are lacking. Encouraging outcomes have been observed with FcRn-inhibitor, efgartigimod in pemphigus. CAR-T cells engineered to target pathogenic B cells hold substantial potential to revolutionize the management of pemphigus, as they are anticipated to induce sustained, long-term remission, or even a potential cure for the disease. Omalizumab appears promising in the treatment of BP.

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Conflicts of interest

There are no conflicts of interest.

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