

# Biologics in autoimmune bullous diseases: Current scenario

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## Abstract

Autoimmune bullous diseases can be intraepidermal (pemphigus group of disorders) or subepidermal (pemphigoid group of disorders). The treatment of these disorders chiefly comprises corticosteroids and immunosuppressant adjuvants like azathioprine and mycophenolate mofetil. Autoantibodies are the main mediators of these diseases. Rituximab, a chimeric anti-CD20 monoclonal antibody targeting B-cells, has emerged as an excellent treatment option for refractory pemphigus vulgaris in the last decade. Since then, many new biologics have been proposed/explored for managing autoimmune bullous diseases. These hold potential for greater efficacy and lesser adverse effects than conventional immunosuppressants. In this review, we discuss the role of various biologics in the treatment of autoimmune bullous diseases, followed by a brief discussion on the drawbacks to their use and new developments in this area.

**Key words:** Autoimmune bullous diseases, biologics, future perspectives, pemphigoid, pemphigus

## Introduction

Autoimmune bullous diseases can be intraepidermal (pemphigus group of disorders) or subepidermal (pemphigoid group of disorders). The introduction of systemic corticosteroids significantly reduced mortality due to pemphigus. The treatment of these disorders is still chiefly dependent on corticosteroids with adjuvants like azathioprine and mycophenolate mofetil. However, the adverse effects resulting from prolonged administration of these drugs remain a concern.

Biologics are defined by the United States Food and Drugs Administration (USFDA) as therapeutic agents derived from any living material (microbes, plants, animals and humans), which either mimic or block the function of naturally occurring proteins. Rituximab, a chimeric monoclonal antibody that targets B-cells expressing membrane-embedded surface molecule CD20 has emerged as an excellent option for the treatment of refractory pemphigus vulgaris in the last decade.<sup>1</sup> Subsequently, many new biologics have been proposed for managing various autoimmune bullous dermatoses. These hold the potential for greater efficacy with lesser adverse effects than conventional immunosuppressants.<sup>2</sup> In this

review, we first discuss the role of various biologics in the treatment of autoimmune bullous diseases, followed by a brief discussion on the drawbacks to their use and new developments in this area.

## Therapies Targeting B-cells CD19, 20 and 22 modulators

Though the potential contribution of T-cells has been explored in recent studies,<sup>3,4</sup> the pathogenesis of autoimmune bullous diseases primarily involves autoantibodies targeting the inter-cellular/matrix adhesion molecules. Since the antibodies are produced by plasma cells derived from B-cells, treatments targeting B-cells are of special interest in autoimmune diseases.

Memory B-cells give rise to short-lived plasma cells that produce pathogenic autoantibodies (in contrast to the long-lived plasma cells that produce antimicrobial antibodies). These memory B-cells and plasma cells have certain surface molecules (stimulatory CD19, 20 and inhibitory CD 22) which can be modulated to modify intracellular signals, causing either depletion of B-cells or inhibiting their proliferation and differentiation [Table 1 and Figure 1].

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Many of these molecules were initially used in lymphomas, rheumatoid arthritis and systemic lupus erythematosus.<sup>5</sup> Subsequently, this was extended to treat pemphigus. Some of these biologics are relatively well-known like rituximab and belimumab (human anti-B-lymphocyte stimulator monoclonal antibody) while others like epratuzumab, blinatumomab and inebilizumab are relatively new.

**Table 1: A summary of various biologics in autoimmune bullous dermatoses**

Therapies targeting B-cells	
Anti-CD20	First generation - Rituximab, ofatumumab, veltuzumab, ocrelizumab Second generation - Tositumomab, obinutuzumab (inhibits stimulatory signals provided by CD20 to memory B-cells, causes depletion of memory B-cells)
Anti-CD19	Blinatumomab, inebilizumab (inhibit stimulatory signals provided by CD19 to B-cells and plasma cells)
CD22 modulators	Epratuzumab (augments inhibitory signals provided by CD-22 to B-cells)
Anti-APRIL	Atacicept
Anti-BAFF	Belimumab
Anti-BAFF receptor monoclonal antibody	VAY736
Bruton tyrosine kinase inhibitors	Ibrutinib (inhibits BCR and FcγR signaling through inhibition of Bruton's tyrosine kinase) PRN1008 PRN 473
CAAR T-cells	Live T-cells that have chimeric autoantibody receptors which are composed of the autoantigen (desmoglein 3 for pemphigus) fused to the signalling domain CD137. These CAAR T-cells recognise autoantigen-specific autoreactive B-cells
Therapies targeting pathogenic antibodies	
FcRn antagonists	Efgartigimod, rozanolixizumab, SYNT001 Intravenous immunoglobulins
Anti-immunoglobulin E monoclonal antibodies	Omalizumab
Therapies targeting cytokines, chemokines and complements	
Anti-complement C1s monoclonal antibody	Sutimlimab
IL-4 receptor antagonist	Dupilumab
Anti-IL-5 monoclonal antibody	Mepolizumab
Anti-eotaxin-1 monoclonal antibody	Bertilimumab
Miscellaneous	
Syk inhibitors	Fostamatinib
IL-17 inhibitor	Ixekizumab
CD40-CD40L inhibition	CD40L/CD154 inhibitors
Polyclonal T-regulatory cells	Can halt initial sensitization of T-cells

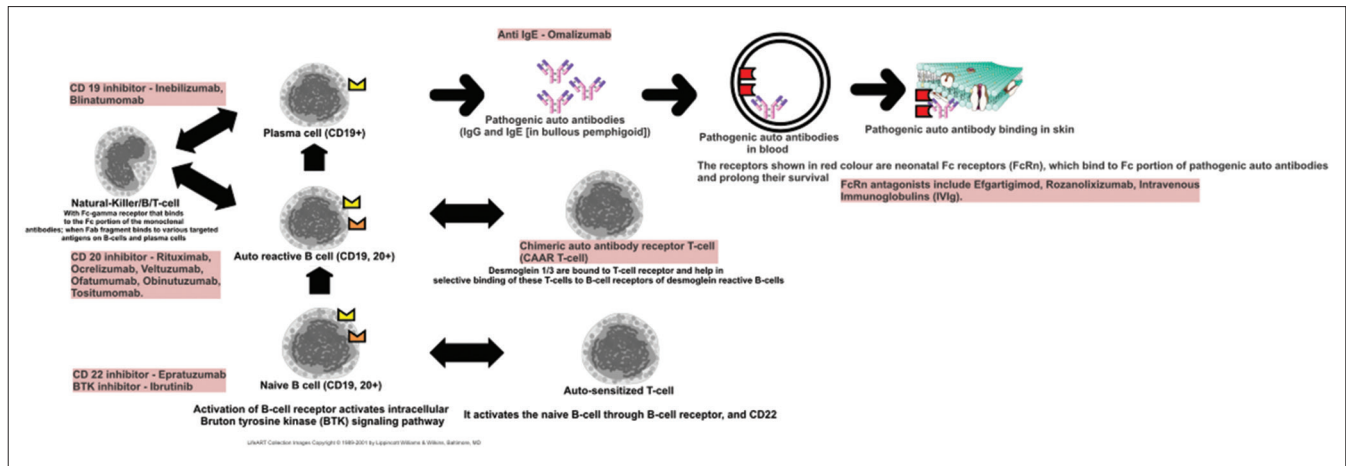
BCR: B cell receptor, FcγR: Receptor for Fc portion of immunoglobulin G, CAAR: Chimeric autoantibody receptor, BAFF: B-cell activating factor, APRIL: A proliferation-inducing ligand, Syk: Spleen tyrosine kinase, FcRn: Neonatal Fc receptor, IL: Interleukin, CD: Cluster of differentiation

CD20 inhibitors are generally classified as first generation (rituximab) and second generation (ocrelizumab, ofatumumab, veltuzumab, obinutuzumab and tositumomab) on the basis of the proportion of the chimeric component in the molecule. Second generation anti-CD20 monoclonal antibodies are humanized and considered to be less immunogenic, and some of these molecules also have the advantage of subcutaneous injection. Anti-CD20 monoclonal antibodies have also been classified on the basis of their primary mechanism of action and functional differences demonstrated *in vitro*, as type I and II. Type I molecules (rituximab, ofatumumab, veltuzumab) cause a redistribution of CD20 into the lipid rafts, and act via both complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Type II molecules (obinutuzumab, tositumomab) do not induce complement-dependent cytotoxicity; rather, these induce a much stronger direct non-apoptotic lysosomal form of programmed cell death mediated by homotypic adhesion (two similar type of cells adhere to each other, which is followed by activation of lysosomes and release of their contents), and a lesser degree of antibody-dependent cell-mediated cytotoxicity.<sup>6</sup>

Ofatumumab, the first second-generation type I anti-CD20 monoclonal antibody, causes even more potent complement-mediated cytotoxicity than rituximab. Though reported to be successful in a recent case report,<sup>7</sup> two therapeutic trials of ofatumumab in pemphigus were prematurely terminated due to commercial reasons (NCT01920477, NCT02613910).<sup>6</sup> Veltuzumab is also a second generation type I anti-CD20 monoclonal antibody which results in significantly more complement-mediated cytotoxicity than rituximab; it can be administered subcutaneously. It was reported to be effective in pemphigus in a case report<sup>8</sup> and was granted orphan drug status for pemphigus by the USFDA in 2015.<sup>6</sup>

Obinutuzumab and tositumomab are second generation type II anti-CD20 monoclonal antibodies. Though obinutuzumab has been granted a breakthrough therapy designation for adult lupus nephritis by USFDA, its use has not yet been explored in pemphigus.<sup>9</sup>

Inebilizumab and blinatumomab are anti-CD19 monoclonal antibodies that have the potential to affect both memory B-cells and plasma cells (plasma cells do not express surface CD20 and are hence not affected by rituximab). CD22 is a co-receptor of the B-cell receptor which inhibits the overactivation of the latter. Epratuzumab is a non-B-cell depleting, humanized monoclonal antibody that augments the normal inhibitory signal generated from CD22.<sup>10-12</sup> Interestingly, epratuzumab also leads to significant reductions in the surface expression of CD19, 21 and 79b on B-cells and results in the transfer of these molecules to NK-cells and T-cells instead (troglodytosis).<sup>13</sup> It has been tried in systemic lupus erythematosus with variable results and may be used in pemphigus in the future.<sup>14,15</sup>



**Figure 1:** A schematic diagram representing the pathway of B-cell sensitization, activation and production of pathogenic antibodies. Also listed are various biologics that act on different steps of this pathway

Secondary impairment in T-cell function which is generally associated with B-cell depletion can explain the usual long-term disease remission induced by B-cell inhibitors, even after B-cell recovery is complete.<sup>16</sup>

B-cell activating factor/B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) belong to the tumor necrosis factor (TNF) superfamily of cytokines. They both support the activation, survival and proliferation of B-cells and plasma cells, and help in maintaining T-cell-independent antibody responses; they differ with respect to the distribution of their receptors.<sup>17</sup> Their levels are positively correlated with systemic manifestations in systemic lupus erythematosus and rheumatoid arthritis. An anti-BAFF monoclonal antibody, belimumab, is approved by the USFDA for the treatment of systemic lupus erythematosus.

B-cell activating factor was found to be elevated in patients having bullous pemphigoid but not in patients having pemphigus. Moreover, its levels rose initially in the disease, followed by a rise in the levels of anti-bullous pemphigoid-180 (anti-BP180) antibodies, though the levels of both did not correlate.<sup>18</sup> In a recent study, B-cell activating factor levels were found to be elevated in endemic Tunisian pemphigus foliaceus but not in pemphigus vulgaris.<sup>19</sup> Further, the levels were significantly higher in those with greater body surface area involvement, recurrent active disease, and those not receiving treatment with corticosteroids.<sup>19</sup>

APRIL was found to be significantly elevated in treatment-naive pemphigus vulgaris patients as compared to patients in remission on treatment and healthy controls in one study.<sup>20</sup> Another study however found APRIL to be elevated in patients having bullous pemphigoid early in their disease (correlated with B-cell activating factor levels) but not in pemphigus patients.<sup>21</sup> In yet another interesting study, it was observed that giving rituximab to pemphigus patients led to a significant elevation in the levels of B-cell activating factor while APRIL and anti-pathogenic (anti-varicella zoster and

anti-Ebstein Barr virus) antibodies remained unaffected; simultaneously there was a significant reduction in the levels of anti-desmoglein antibodies, suggesting a differential effect of rituximab on different B-cell populations and their proliferation ligands.<sup>22</sup>

#### Bruton's tyrosine kinase inhibitors

Bruton's tyrosine kinases are non-receptor tyrosine kinases that mediate signal transduction inside B-cells and plasma cells following the binding of activating molecules on surface B-cell receptors or Fcγ receptors. Inhibiting B-cell receptor signalling through Bruton's tyrosine kinase inhibitors is a promising concept in the management of autoimmune bullous diseases. A patient having chronic lymphocytic leukemia with paraneoplastic pemphigus and multiorgan involvement responded favorably to ibrutinib.<sup>23</sup> An oral molecule PRN473 (with reversible Bruton's tyrosine kinase inhibitor activity) was found to be beneficial in canine pemphigus foliaceus.<sup>24</sup> Another oral molecule PRN1008 showed impressive results in an open label phase II study with >50% of patients achieving disease control within four weeks of initiating treatment, and is currently undergoing a phase III clinical trial in pemphigus.<sup>25</sup>

#### Chimeric auto-antibody receptor T-cells

Chimeric antigen receptor T-cells were initially developed as potential antitumor therapies. These were patient-derived T-cells engineered *in vitro* to have tumor-antigen binding fragments of monoclonal antibodies directly fused to their signal activating machinery such as the zeta (ζ) chain of CD3, with additional linking to certain co-stimulatory molecules in the second and third generation chimeric antigen receptor T-cells, thus dissociating antigen recognition from major histocompatibility complex (MHC) restriction.<sup>26</sup>

Chimeric auto-antibody receptor T-cells were subsequently engineered as a potential treatment option for autoimmune diseases by generating chimeric immunoreceptors on their surface composed of the putative autoantigen fused to

intracellular domains.<sup>27</sup> Such T-cells are able to specifically kill the culprit B-cells via engagement of B-cell receptors. These receptors bind to the autoantigen present on the chimeric auto-antibody receptor T-cells, activating the T-cells and culminating in the killing of the pathogenic antibody-producing B-cells. Ellebrecht *et al.* demonstrated that chimeric auto-antibody receptor T-cells engineered with the autoantigen desmoglein-3 exhibited specific cytotoxicity against B-cells having anti-desmoglein 3 B-cell receptor *in vitro*. They also demonstrated *in vivo* in a mouse model that such chimeric auto-antibody receptor-expressing T-cells were able to expand and specifically eliminate anti-desmoglein 3 B-cell receptor-expressing B-cells.<sup>27</sup> Notably, these T-cells did not bind free anti-desmoglein antibodies. Since these T-cells were able to form memory T-cells, their activity against the pathogenic B-cells should be persistent.<sup>27</sup> Moreover, to manage a possible epitope spreading, these chimeric auto-antibody receptor-expressing T-cells could also be engineered to express both desmoglein 1 and 3 on their surface.

### Therapies Targeting Pathogenic Autoantibodies Neonatal Fc receptor antagonists

Targeting the neonatal Fc receptor (FcRn, Brambell receptor) forms the basis of the development of many new therapeutics.<sup>28</sup> This receptor is encoded by the *Fcgrt* gene and it resembles an MHC type 1 molecule. It binds to the constant fragment (Fc) of immunoglobulin G (IgG) antibodies leading to their transport inside the cell (transcytosis), thus preventing their degradation and prolonging their half-life significantly.<sup>29</sup> It is strongly expressed on the placenta and helps in transfer of maternal antibodies to the fetal compartment. As a corollary, these neonatal Fc receptors can also bind to pathogenic IgG antibodies resulting in increased half-lives and decreased catabolism of such antibodies; neonatal Fc receptors are therefore implicated in autoimmune diseases. Keratinocytes express neonatal Fc receptors, and knock-out mice lacking these receptors did not develop acantholysis even after passive transfer of anti-desmoglein antibodies.<sup>16</sup>

The potential of neonatal Fc receptors to prolong the half-life of antibodies has been therapeutically exploited to shorten the half-life of pathogenic ones.<sup>30</sup> Efgartigimod (neonatal Fc receptor antagonist) is an engineered Fc fraction of immunoglobulin G1(IgG1) which saturates the neonatal Fc receptors, and therefore causes rapid degradation and clearance of pathogenic antibodies.<sup>31</sup> The result here is similar to that with other methods that remove pathogenic antibodies, like immunoadsorption and plasma exchange but this method is novel.<sup>32</sup> The action is specifically on IgG. No serious adverse effects viz. increased infection risk etc. were noted in healthy volunteers. The lack of infections noted with neonatal Fc receptor-antagonists might be explained by the fact that they can only reduce IgG levels by about 75% whilst sparing other types of antibodies. It might be noted here that the saturation of FcRn and the resulting rapid clearance of antibodies is considered one of the most important therapeutic mechanisms of intravenous immunoglobulins (IVIg). Efgartigimod has

already been used successfully in myasthenia gravis<sup>33</sup> and a phase two study has found encouraging results of its use in six patients of mild to moderate pemphigus (disease control achieved in three patients in one week and in one patient in four weeks; two patients had progression of disease).<sup>32</sup>

Rozanolixizumab is a monoclonal antibody developed against neonatal Fc receptors and has shown promising IgG-reducing properties in healthy volunteers.<sup>32</sup>

### Omalizumab

IgG autoantibodies against bullous pemphigoid antigen 2 (BPAg2, BP180) have long been known to be pathogenic. Recently focus has also been directed at the presence of IgE autoantibodies directed against BP180.<sup>34,35</sup> It was seen in a recent study that these IgE-BP180 antibodies did not increase the sensitivity of diagnosis of bullous pemphigoid but their levels had a significant correlation with disease activity.<sup>36</sup> A meta-analysis concluded that severity of bullous pemphigoid was correlated with serum IgE levels, though the disease phenotype was not.<sup>37</sup>

Omalizumab binds to the circulating IgE levels, and thus decreases the free IgE levels, thereby decreasing the IgE bound to cell surfaces (basophils, mast cells and eosinophils), which in turn decreases the expression of the receptor for Fc portion of IgE on the said cells (FcεR1). There are multiple case reports and two small case series that have demonstrated the efficacy of omalizumab in bullous pemphigoid.<sup>38,39</sup> A systematic review has noted an 84% complete response rate with omalizumab, though a relapse rate of 80% was also noted after a mean interval of 3.2 months.<sup>40</sup> Interestingly, there are reports of patients with rituximab-refractory bullous pemphigoid responding to omalizumab and vice versa, indicating the intricacies of the types of autoantibodies, their specific pathogenic actions and wide inherent inter-individual variations in this disease.<sup>41-43</sup> Omalizumab has also been used successfully in the treatment of infantile bullous pemphigoid.<sup>44</sup>

### Inhibiting Cytokines, Chemokines and Complements Dupilumab, bertilimumab and mepolizumab

The presence of eosinophils in the dermis and subepidermal clefts is considered a hallmark of bullous pemphigoid. Peripheral blood eosinophilia is observed in 5-43% of patients with bullous pemphigoid.<sup>45</sup> Activated eosinophils have been shown to cause splitting at the dermoepidermal junction by releasing eotaxin-1 and other granular contents in the presence of pathogenic autoantibodies.<sup>45</sup> Eosinophilic infiltration in the skin is mediated by IL-4 and IL-5, the cytokines found elevated in the skin and sera of patients with bullous pemphigoid.<sup>45</sup>

Phase two trials studying IL-5 antagonist mepolizumab and anti-eotaxin-1 antibody bertilimumab in bullous pemphigoid have been completed. Mepolizumab failed to control the disease, whereas bertilimumab had an appreciable steroid-



sparing effect and resulted in 84% reduction in disease severity.<sup>46</sup> Dupilumab, an IL-4 receptor antagonist, was also reported to be effective in recalcitrant bullous pemphigoid in a case report.<sup>47</sup>

Complement activation plays an important role in the pathogenesis of bullous pemphigoid. Sutimlimab, an anti-C1s monoclonal antibody, is being evaluated for its effectiveness in bullous pemphigoid.<sup>46</sup>

#### Miscellaneous

Other potential targets in bullous pemphigoid include the chemoattractant receptor-homologous molecule, a prostaglandin D2 receptor which is thought to promote activation and recruitment of Th2 cells and eosinophils;<sup>45</sup> and the Th-17 pathway involving IL-17.<sup>46</sup> An ongoing trial is assessing the effect of ixekizumab, a humanized IL-17A antagonist, in bullous pemphigoid. Spleen tyrosine kinase and leukotriene-B4 inhibition are also potential therapeutic targets in pemphigoid diseases.<sup>25</sup> In fact, spleen tyrosine kinase has emerged as an important non-receptor tyrosine kinase mediating inflammation in an *in vivo* mouse model of epidermolysis bullosa acquisita,<sup>48</sup> and the same was demonstrated in a whole-genome analysis of the mouse skin in an experimental model of epidermolysis bullosa acquisita.<sup>49</sup> Spleen tyrosine kinase inhibitors (like fostamatinib) could perhaps be employed in the treatment of the pemphigoid group of disorders, especially those with mechano-bullous characteristics.<sup>48</sup>

In the complex milieu of T and B-cells in pemphigus, T-cell sensitization initiates and propagates antibody production.<sup>50</sup> This Th-cell and B-lymphocyte cross-talk primarily occurs through CD40-CD40L (CD154), and can be modulated.<sup>51</sup> A previous study assessed the role of CD40L blocker, and concluded that blocking CD40L could prevent the formation of pathogenic antibodies in a mouse model of pemphigus.<sup>52</sup> Polyclonal T-regulatory cells can be employed to inhibit autoreactive T-helper cells and B-lymphocytes, and phase I trials in pemphigus are ongoing to assess the potential of polyclonal T-reg administration.<sup>25</sup>

It has been suggested that the generous collection of desmoglein-specific B-cells in the skin in pemphigus renders significant interactions amongst multiple cell types including IL-21 and IL-17A producing T-cells. IL-21 activates Janus-associated kinases (JAKs) JAK1 and JAK3. A possible therapeutic role of tofacitinib (pan-JAK inhibitor) in pemphigus has been recently proposed.<sup>53</sup>

### Current Status of Biologics in Pemphigus and the Pemphigoid Group of Disorders

#### Pemphigus group of disorders

Meta-analyses have established the efficacy of rituximab in pemphigus.<sup>54,55</sup> Though initially used in pemphigus refractory to conventional treatments, a recent prospective study has

established the efficacy of rituximab in newly diagnosed moderate to severe pemphigus as a first-line treatment, in combination with a short duration of prednisolone.<sup>56</sup> Not only was the efficacy better, but the cumulative dose of corticosteroids and adverse effects were also significantly lower in the combination group (rituximab plus short duration prednisolone) than in the monotherapy (conventional doses of prednisolone alone) group.<sup>57</sup> Rituximab was approved by the USFDA for pemphigus vulgaris in 2018,<sup>58</sup> and an international panel of experts recommended it as a first-line treatment in moderate to severe pemphigus.<sup>59</sup> It has also been used successfully in childhood and juvenile pemphigus.<sup>60</sup> Interestingly, though pemphigus herpetiformis is an IgG-mediated disease, it did not respond to rituximab in a retrospective study.<sup>61</sup>

Ahmed and Shetty, in their meta-analysis, showed that significant clinical control was achieved within six weeks in 90–95% of pemphigus patients treated with rituximab plus low-dose corticosteroids or other immunosuppressive agents, with complete remission being achieved in 3–4 months on treatment.<sup>55</sup> They concluded that patients receiving rituximab as per the rheumatoid arthritis protocol were more likely to achieve complete remission and remain off treatment post-rituximab.<sup>55</sup> The largest retrospective Indian study that included 146 patients treated with a uniform rheumatoid arthritis protocol showed that complete remission off treatment could be achieved in 73.3% of the patients in 6.6 months, which was sustained for 9.1 months before relapse. Relapse was seen in 76.5% of patients.<sup>62</sup> Time taken to achieve remission was significantly longer in pemphigus foliaceus than in pemphigus vulgaris. Another retrospective review by Heelan *et al.* demonstrated rituximab used in rheumatoid arthritis protocol to be a cost-effective treatment in comparison to high dose IVIg in pemphigus.<sup>63,64</sup>

#### Pemphigoid group of disorders

Overall, rituximab has been found to be beneficial in the pemphigoid group of disorders, though its efficacy therein is generally lower and it takes longer to achieve complete remission than in the pemphigus group of disorders. The efficacy also seems better in bullous pemphigoid than in mucous membrane pemphigoid or epidermolysis bullosa acquisita. A retrospective study reporting the outcomes in 28 patients (8 with bullous pemphigoid, 14 mucous membrane pemphigoid, 5 epidermolysis bullosa acquisita and one with linear IgA dermatosis) who received rituximab on day 1 and 15 (500 mg each in six patients and 1 g each in 22 patients) observed disease control, partial remission and complete remission in 67.9%, 57.1% and 21.4% of the patients at 14.5, 34.2 and 59.2 weeks respectively.<sup>65</sup>

#### Combination with intravenous immunoglobulins

Combination treatment with rituximab and intravenous immunoglobulins was employed in 12 patients of severe refractory bullous pemphigoid (mean age, 68 years) in a study.<sup>66</sup> Clinical remission on treatment was achieved in 4.6 months and

all previous treatments could be stopped in 6.2 months. Patients were followed for a mean of 73.8 months without any adverse effects being noted. Only two patients relapsed, and their disease responded to repeat rituximab infusions.

#### Comparison with omalizumab

A recent systematic review and meta-analysis of the use of omalizumab and rituximab in bullous pemphigoid (84 patients; 62 treated with rituximab and 22 with omalizumab) concluded that both were equally safe and efficacious, with complete response rates of 84% and 85% respectively, and adverse effects in 20% and 24% respectively. However patients treated with rituximab had significantly lower rates of recurrence (29% with rituximab vs 80% with omalizumab) and a significantly longer disease-free period until relapse occurred (10.2 months with rituximab vs 3.4 months with omalizumab).<sup>40</sup> This is expected based on how the drugs work. However, omalizumab may be better suited for elderly patients with bullous pemphigoid having comorbidities including diabetes mellitus and other immunocompromised states.

#### Biosimilars

Despite the undeniable efficacy of biologics, their cost has always remained a concern; this has led to the development of 'biosimilars'. A biosimilar, though not an exact replica of the original biologic molecule, is considerably similar to the latter, with comparable efficacy and adverse effect profile. Differences arise because of inherent variations in the cell lines and purification systems used, and post-translational modifications thereafter. Biosimilars of rituximab have been used in India with good results.<sup>67</sup>

#### Pitfalls of Current Treatment Strategies with Rituximab

Although encouraging, the use of biologics, especially rituximab, in pemphigus and the pemphigoid group of disorders is currently associated with certain shortfalls that include the following:

- Resistance and treatment failure
- Relapse
- Lack of clarity on optimal dosing
- Infections
- Route of administration

#### Resistance and treatment failure

Resistance to rituximab can be primary or secondary. Secondary resistance refers to reduced efficacy after initial successful infusions.<sup>68</sup> The following factors have been postulated to cause resistance to rituximab. Many of these are well-studied in malignancies (where multiple infusions of rituximab are usually required) but not in pemphigus.

- a. Apart from inducing hypersensitivity infusion reactions, the murine component in rituximab might also be associated with the formation of human anti-chimeric antibodies that may adversely affect the outcome of subsequent infusions by neutralizing the administered rituximab.<sup>16</sup>

- b. Most therapeutic monoclonal antibodies are of the IgG type. The Fc fragment of these antibodies binds with Fc $\gamma$  receptors present on macrophages, dendritic cells, B-cells and NK-cells (maximum expression is seen on the cells of innate immune system) while the Fab fragment binds to CD20 expressed on B-cells. This interaction leads to the neutralization of the target opsonized by the IgG (antibody-dependent cell-mediated cytotoxicity). Fc $\gamma$  receptors have a multitude of actions, usually stimulatory but sometimes inhibitory (in humans, Fc $\gamma$ RI, Fc $\gamma$ RIIa [CD32a], Fc $\gamma$ RIIc [CD32c], Fc $\gamma$ RIIIa [CD16a] and Fc $\gamma$ RIIIb[CD16b] are stimulatory, while Fc $\gamma$ RIIIb[CD32b] is inhibitory).<sup>69,70</sup> Stimulatory Fc $\gamma$  receptors activate the killing of opsonized targeted cells by macrophages or NK-cells whereas inhibitory Fc $\gamma$  receptors inhibit this process. Polymorphisms in these receptors could affect antibody-dependent cell-mediated cytotoxicity and therefore outcomes of rituximab infusions. Such polymorphisms might be responsible for the primary rituximab resistance in some patients.<sup>71-73</sup> However, polymorphisms in Fc $\gamma$ RIIIa or Fc $\gamma$ RIIa did not influence treatment outcomes in patients having follicular lymphoma treated with rituximab in one study.<sup>74</sup> Overall, findings in this area have been inconsistent,<sup>74</sup> and more studies regarding these molecules are needed, especially in pemphigus.<sup>75</sup>
- c. Type I anti-CD20 monoclonal antibodies like rituximab have been shown to undergo internalization in the phagocytosing cells along with the CD20 molecule (a process known as trogocytosis) mediated by Fc $\gamma$  receptors.<sup>68</sup> Due to a reduction in the number of available CD20 receptors, this phenomenon can decrease the efficacy of subsequent infusions of CD20 inhibitors, and in fact has been associated with reduced survival and treatment response in patients with hematologic malignancies.<sup>68</sup> How trogocytosis is relevant to an autoimmune disease such as pemphigus needs to be studied in detail.<sup>76</sup>
- d. Another reason for resistance to rituximab could be long-lived plasmablasts (lacking CD20) producing anti-desmoglein antibodies. These cells can be effectively targeted using anti-CD19 antibodies, like blinatumomab and inebilizumab.<sup>16</sup>
- e. Site-specific factors may be important in determining the response to rituximab. Clinical experience has suggested that despite appreciable response to rituximab elsewhere on the body, some patients have persistent lesions at a few sites such as the scalp and oral cavity. It would be of interest to look at the factors responsible for relative rituximab resistance at these poorly responding sites. Some clinical factors determining the persistence of lesions in oral cavity have been described before including the presence of deep/ crateriform ulcers, presence of the lesions

on the retromolar trigone or the line of occlusion of the buccal mucosa, longer duration of disease and presence of lichenoid hue.<sup>77</sup> It has been observed that the expression of desmoglein 3 is substantial in the scalp and buccal mucosa; this could possibly lead to a persistent immune response and treatment-refractory lesions at these sites.<sup>78</sup>

Further, it has been seen that addition of autologous serum to rituximab helped significantly in attaining anti-tumor response in central nervous system lymphomas, probably due to the addition of complement at a site normally deficient in immunocytes and complement.<sup>79</sup>

- f. Though neonatal Fc receptors (FcRn) are known to potentiate the half-life of pathogenic autoantibodies, these receptors can also bind to administered monoclonal antibodies increasing their half-life. It remains to be seen if deactivating mutations in the *Fcgrt* gene encoding FcRn can cause an increased catabolism of administered monoclonal antibodies and therapeutic failure in some individuals.
- g. CD20 transcript variants with less inherent binding to rituximab have been proposed to explain rituximab resistance in B-cell malignancies. Though these variants could not be found in pemphigus and rheumatoid arthritis patients, future research may reveal novel CD20 transcript variants that could impart primary rituximab resistance.<sup>80,81</sup>
- h. Treatment failure and early relapse after rituximab have been associated with prior prolonged treatment with conventional immunosuppressives.<sup>82</sup> Late introduction of rituximab for management might mean more pathogenic B-cell clones have had time to develop.<sup>82</sup>
- i. A new subset of B-cells that produce interleukin-10 (also known as B-regulatory cells) and negatively regulate autoimmunity has been recently described. It is worth noting that the depletion of these B-regulatory cells (along with significant depletion of pathogenic B-cells) after treatment with biologics can cause a paradoxical flare of the autoimmune process.<sup>5</sup>

#### Relapse after rituximab therapy and factors determining it

Positive anti-desmoglein 3 titres and direct immunofluorescence are associated with an increased risk of relapse in pemphigus.<sup>83</sup> Apart from these, factors specifically related to an early relapse after treatment with rituximab have been elucidated in a few studies. One study demonstrated a higher relapse rate in patients who had a longer duration of disease and received rituximab after being refractory to conventional treatment agents than those who received it as the first-line agent.<sup>84</sup> However, no effect was seen on relapse rates in another study where rituximab was administered to immunosuppressant-naive and immunosuppressant-refractory patients, but the rates of complete remission off treatment were higher in immunosuppressant-naive patients receiving rituximab, even after adjusting for disease

duration.<sup>85</sup> Yet another study demonstrated an increased relapse rate and a reduced rate of complete remission in patients receiving rituximab as per the low-dose rheumatoid arthritis protocol (500 mg, 2 doses, 15 days apart) and those with a longer duration of disease. This study also demonstrated reduced relapses in patients receiving plasma exchange and immunoadsorption.<sup>86</sup>

#### Choosing between ultra-low, low and high dose protocols of rituximab

In pemphigus, rituximab was initially employed in lymphoma protocol (375 mg/m<sup>2</sup>). This was followed by reports of a successful outcome with low-dose protocols (1g or 500mg, 15 days apart).<sup>87</sup> A meta-analysis by Wang *et al.* showed that there were no differences in remission and relapse rates between high ( $\geq 2000$  mg/ cycle) and low dose (<1500 mg/ cycle) protocols, or between rheumatoid arthritis and lymphoma protocols, but the remission lasted longer with high-dose protocols.<sup>54</sup> Another study showed no difference in the remission rates on the standard rheumatoid arthritis protocol (1 g, 2 doses, 15 days apart) and the lymphoma protocol, but the low-dose rheumatoid arthritis protocol (500 mg, 2 doses, 15 days apart) was associated with reduced rates of complete remission.<sup>85</sup> A more recent study also associated the lymphoma protocol of rituximab and older age with the attainment of complete remission off treatment in pemphigus.<sup>88</sup>

Since the burden of autoreactive B-cells in pemphigus is significantly less than that of neoplastic B-cells in hematologic malignancies, it seems prudent to employ lower doses of rituximab in pemphigus.<sup>89</sup> A recent study has demonstrated 68%, 74% and 97% reductions of B-cell counts in healthy volunteers following 0.1, 0.3 and 1 mg/m<sup>2</sup> dosage of rituximab respectively. B-cell recovery was 60% in the 1 mg/m<sup>2</sup> group at four weeks and almost complete in the 0.1 mg/m<sup>2</sup> and 0.3 mg/m<sup>2</sup> groups at the same time.<sup>90</sup> This finding in healthy volunteers should pave the way for well-designed clinical trials assessing the efficacy of ultra-low-dose rituximab in patients of pemphigus. By extrapolating the data of this study, the authors have proposed a regimen of 100 mg rituximab, two doses, three months apart, to be sufficient to cause B-cell depletion for six months. This approach apart from being cost-friendly is also attractive owing to a probably lesser resultant immunosuppression.<sup>89</sup>

#### Infections

Though clinical experience suggests that rituximab is remarkably safe with infusion reactions being the commonest reported complications, infections, late-onset neutropenia and septicemia after rituximab infusions can sometimes be life-threatening, especially with the high-dose protocols.<sup>91</sup> Therefore, some precautions should be routinely followed, including screening for hepatitis B and C, HIV and uncontrolled diabetes; up to date vaccinations before starting rituximab; and prophylaxis for *Pneumocystis carinii*



pneumonitis after rituximab infusion.<sup>92</sup> Guidelines strongly recommend prophylactic immunization with non-live vaccines for patients of autoimmune bullous disorders in whom biologic therapies are planned.<sup>93</sup>

High-dose intravenous immunoglobulins (IVIg) have been successfully used in severe pemphigus.<sup>94-96</sup> Ahmed *et al.* have reported a protocol combining rituximab and IVIg with no infectious complications or loss of efficacy in ten patients. They proposed that the loss of antibodies (pathogenic autoantibodies and normal immunoglobulins) brought about by rituximab is compensated by the addition of non-pathogenic normal immunoglobulin in IVIg, when using these in combination.<sup>97</sup>

#### Routes of administration

Rituximab is traditionally administered intravenously. Intravenous administration requires the patients to stay in the hospital for a longer time. Subcutaneous route, apart from being simpler, is less painful and requires a shorter stay in the hospital. Subcutaneous rituximab, manufactured using recombinant hyaluronidase, was non-inferior to the intravenous form in studies performed for various lymphomas, better tolerated by patients and was approved by the USFDA in 2017 for the same.<sup>98</sup> Many of the second generation CD20 inhibitors have the advantage of subcutaneous administration which would result in better patient tolerance and less time consumption for patients and office staff alike.

Intralesional administration of rituximab in a dose of 5 mg/cm<sup>2</sup> (2 such doses, 15 days apart) has also been attempted by Vinay *et al.* and found to be beneficial. This minimal dosage was also associated with an almost complete decline in CD19 cells in the blood.<sup>99</sup>

#### Future

An optimal regimen of rituximab for autoimmune bullous disorders needs to be established. The benefits, hazards and cost-effectiveness of combination treatments (especially rituximab with intravenous immunoglobulins, omalizumab and other immunosuppressants) need to be studied. The future might also lie in further exploring the genetic bases and therapeutic modulation of antibody checkpoints (FcγRs), including prediction of treatment failure or resistance in those harbouring inhibitory polymorphisms. Research is also ongoing regarding the efficacy of new molecules inhibiting downstream pathways in acantholysis, like p38 mitogen-activated protein kinase (MAPK) inhibitors, and signal transducers and activators (STAT3) inhibitors.<sup>100</sup> Much translational research is under way and the future of biologics in autoimmune bullous dermatoses looks bright.

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#### Conflicts of interest

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