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REVIEW

Biological therapy of autoimmune blistering diseases

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ABSTRACT

Introduction: Autoimmune blistering skin diseases are a group of disorders subdivided according to the location of blister formation: intraepidermal blistering in the pemphigus group and subepidermal in the pemphigoid group. These conditions are clinically heterogeneous and are treated with systemic corticosteroids and/or other forms of immunosuppression on the basis of clinical subtype and disease severity. These approaches may not be effective for the induction and maintenance of clinical response or need to be stopped because of intolerable side effects.

Areas covered: Biological therapies can represent a valid alternative strategy in various autoimmune blistering disorders and this review article will address this issue with a special focus on pemphigus vulgaris and bullous pemphigoid. These biological approaches are designed to target B cells, autoantibodies, complement proteins, and several cytokines.

Expert opinion: Innovative strategies for the treatment of autoimmune blistering conditions primarily depend on the use of drugs with a high degree of specificity targeting crucial steps in the immunopathology of these disorders. Novel biological agents offer treatment alternatives to patients with autoimmune blistering conditions by targeting B cells, pathogenic autoantibodies, complement and cytokines.

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Autoimmune blistering diseases; pemphigus vulgaris; pemphigoid; biological agents; autoimmunity

1. Autoimmune blistering diseases

Autoimmune blistering skin diseases are a group of conditions subdivided according to the location of blister formation: intraepidermal blistering in the pemphigus group and subepidermal in the pemphigoid group (Table 1) [1–5]. Pemphigus vulgaris (PV) is the most prevalent member of the pemphigus group and is a potentially life-threatening skin disease. PV is characterized by circulating autoantibodies targeting the desmosomal cadherins, desmoglein (DSG) DSG3, and sometimes DSG1, resulting in disruption of desmosomes and loss of intercellular adhesion (also known as acantholysis) in skin and mucous membranes [6,7]. Bullous pemphigoid (BP) is the most common disorder within the pemphigoid group and is characterized by circulating autoantibodies directed against two components of the basement membrane zone of the epithelium, BP180 and BP230. BP is less severe than PV and is mainly observed in elderly people [8–10].

These conditions are generally managed with systemic corticosteroids which are often utilized in combination with other forms of immunosuppression most often azathioprine or mycophenolate, although only a few randomized clinical trials have proven their efficacy. Treatment can be augmented with plasmapheresis which aims to reduce circulating autoantibody levels or intravenous immunoglobulin (Ig) which acts by several mechanisms including dilution of autoantibody levels. These approaches may not be effective for the induction and maintenance of clinical response or need to be stopped because of intolerable side effects. Biological therapies can represent a valid alternative strategy in various autoimmune blistering disorders and this review article will address this issue with a special focus on PV and BP.

2. Targeting B cells

The role of B cells in the pathogenesis of autoimmune blistering diseases involves different cellular functions, including secretion of autoantibodies, T-cell help, and pro-inflammatory cytokine production [11,12]. Consequently, B cells are an important therapeutic target in these disorders (Table 2) and selective depletion of B cells using monoclonal antibody (mAb) therapy is a well-established treatment of autoimmune blistering diseases [13]. The most common mAb utilized to treat these disorders is rituximab which is a chimeric mAb specific for the transmembrane protein CD20 on B cells [14]. Rituximab has demonstrated safety and efficacy in patients with autoimmune blistering skin disorders refractory to conventional immunosuppressive treatments [15]. In particular, a recent study indicates that rituximab at the dosage of 1000 mg on days 0 and 14 plus 500 mg at months 12 and 18 associated with 0.5–1 mg/kg of prednisone tapered over 3–6 months should be considered the first-line treatment in newly diagnosed moderate-to-severe PV [16]. Although more effective results are obtained using high dose of rituximab instead of low dose [17,18], a recent study provides the rationale for the utilization of an ultralow dosage of rituximab (two doses of 100 mg every 3 months) for a 6-month depletion of the B-cell population [19,20]. However, prolonged B-cell depletion may significantly

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Article highlights

- Selective depletion of B cells is a well-established treatment autoimmune blistering diseases.
- Rituximab associated with short-course prednisone should be considered the first-line treatment in newly diagnosed moderate-to-severe pemphigus.
- Alive T cells that express a chimeric autoantibody receptor (CAAR-T cells) are able to deplete anti-DSG3-specific B cells *in vitro* and in a pemphigus mice model.
- BP patients can be treated successfully with omalizumab, an anti-IgE mAb.
- Targeting the neonatal Fc receptor for reducing pathogenic IgG autoantibodies is an attractive option for the treatment of autoimmune blistering conditions.

This box summarizes key points contained in the article.

increase the risk of infection although studies suggest that rituximab mainly acts on memory B cells that give rise to short-lived plasma cells responsible for the production of pathogenic autoantibodies and not on long-lived $CD20^-$ plasma cells which produce protective antimicrobial antibodies [21]. On the other hand, rituximab has an immunosuppressive effect also on antigen-specific T cells, though it does not affect overall T-cell number and function [22]. Taken together, these observations have increased the need for specific targeting of pathogenic B cells in order to avoid undesired immunosuppression. To this regard, several therapies targeting alternative B-cell surface markers, CD22, CD19, CD40, and CD40 ligand, might be evaluated. CD19 is an Ig superfamily surface glycoprotein of 95 kDa that is expressed in all stages of B-cell development including plasma cells [23]. This characteristic makes CD19 an attractive therapeutic target and several anti-CD19 agents have been developed, notably blinatumomab and inebilizumab [24,25]. Blinatumomab is a bispecific mAb that binds simultaneously to both CD3-positive cytotoxic T cells and CD19-positive B cells. At present, it is utilized in order to recognize and eliminate CD19-positive acute lymphoblastic leukemia blasts, but it is characterized by elevated toxicities and consequently does not appear to be suitable for a potential use in autoimmune blistering conditions [26]. Inebilizumab is a humanized, afucosylated IgG1κ mAb that specifically depletes CD19-expressing B cells by means of antibody-dependent cell-mediated cytotoxicity including plasma cells which are not affected by treatment with anti-CD20 mAb. Inebilizumab showed an acceptable safety profile in patients with multiple sclerosis and consequently may deserve consideration for a future utilization in severe forms of autoimmune blistering diseases [27].

Epratuzumab is a humanized B-cell-directed nondepleting mAB that targets CD22 which has been investigated in patients with systemic lupus erythematosus (SLE) [28]. Epratuzumab enhances the normal inhibitory role of CD22 on B-cell function with the consequent reduction of B-cell effector mechanisms. The drug was well-tolerated and could be an interesting approach for the treatment of autoimmune blistering diseases in the future [28].

An alternative approach to mAbs in order to target B cells is represented by alive T cells that express a chimeric autoantibody receptor (CAAR-T cells) composed of the PV autoantigen DSG-3 fused to the signaling domains of CD137 and CD3ζ engineered to recognize DSG3-specific B cells [29]. A recent investigation has demonstrated that CAAR-T cells are able to deplete anti-DSG3-specific B cells *in vitro* and in a pemphigus

Table 2. B-cell targeted approaches for the treatment of autoimmune bullous disorders.

B-cell targeted approaches in autoimmune bullous disorders	Mechanism of action
Anti-CD20 monoclonal antibodies (e.g. rituximab)	Blockade of memory B cells that give rise to short-lived plasma cells (Ref. [14])
Anti-CD19 monoclonal antibodies (e.g. blinatumomab and inebilizumab	Blockade of CD19-expressing B cells including plasma cells (Refs. [24] and [25])
Anti-CD22 monoclonal antibody (epratuzumab)	Enhancement of the normal inhibitory role of CD22 on B-cell function (Ref. [28])
CAAR-T cells	Depletion of anti-DSG3-specific B cells (Ref. [29])

Table 1. Main subtypes of pemphigus and pemphigoid and target antigens.

Pemphigus group	Target antigens	Pemphigoid group	Target antigens
Pemphigus vulgaris	DSG3, DSG1	Bullous pemphigoid	BP180, BP230
Pemphigus vegetans	DSG3, DSG1	Dermatitis herpetiformis	Epidermal transglutaminase
Pemphigus foliaceus	DSG1	Mucous membrane pemphigoid	BP180
			BP230
			Integrin subunits α6/β4
			Laminin-5
			Laminin-6
			Type VII collagen
Endemic pemphigus foliaceus	DSG1	Linear IgA bullous dermatosis	LAD-1
Pemphigus erythematosus	DSG1	Herpes gestationis	BP180
Paraneoplastic pemphigus	DSG3	Epidermolysis bullosa acquisita	Type VII collagen
	DSG1		
	BP180		
	Plectin		
	Desmoplakin I		
	Desmoplakin II		
	Envoplakin		
	Periplakin		
IgA pemphigus	Desmocollin 1 (subcorneal type)	Lichen planus pemphigoid	BP180

Table 3. Targeted therapies against autoantibodies involved in autoimmune bullous disorders.

Targeted therapies against autoantibodies	Mechanism of action
Human IgG1 Fc-fragment against the neonatal Fc receptor (efgartigimod)	Blockade of the interaction of neonatal Fc receptor with IgGs and subsequent inhibition of IgGs rescue and recycling (Ref. [31])
Monoclonal antibody against the high-affinity receptor binding site on human IgE (omalizumab)	Blockade of IgE anti-BP180 antibodies (Refs. [38–40])
Immunoadsorption	Removal of total IgG from patient plasma (Ref. [45])
Intravenous immunoglobulins	Neutralization of endogenous antibodies by anti-idiotype antibody production, Fc receptors modulation, and reduction in half-life of autoantibodies (Ref. [48])

Table 4. Targeted therapies against cytokines and chemokines in autoimmune bullous disorders.

Cytokines and chemokines targeted therapy	Mechanism of action
Fusion protein and monoclonal antibodies against anti-TNF-alpha (e.g. etanercept and infliximab)	Blockade of human TNFα (Refs. [67] and [70])
Monoclonal antibody against IL-12/IL-23 (ustekinumab)	Blockade of IL-12-induced Th1 cell activation and IL-23-induced Th17 cell effector function (Refs. [78] and [79])
Monoclonal antibodies against BAFF and APRIL (e.g. atacicept and belimumab)	Inhibition of activation and proliferation of B cells (Ref. [81])
Bertilimumab is a fully human IgG4 mAb against eotaxin-1	Blockade of eosinophil homing and migration into tissues (Ref. [91])

BAFF: B-cell activating factor; APRIL: a proliferation-inducing ligand.

mice model [29]. Anti-DSG3 is the main pathogenetic antibody in PV and consequently, this approach could potentially eliminate only the pathogenic autoreactive B-cell population. Moreover, this approach produced long-term memory CAAR-T cells that can potentially determine maintenance of remission. On the other hand, several other autoantibodies are present in patients with PV, with an unknown extent of pathogenicity, and, consequently, may affect the translational application of this technology [30].

3. Targeting autoantibodies

Methods for direct targeting of pathogenic autoantibodies could be attractive options for the treatment of autoimmune blistering conditions (Table 3).

Efgartigimod is a human IgG1 Fc-fragment that has been engineered to increase its affinity for the neonatal Fc receptor (FcRn) [31]. High concentrations of pathogenic IgG autoantibodies in autoimmune conditions may occur due to the effect of the FcRn that bind to IgGs inhibiting their degradation [32]. Efgartigimod blocks the interaction of FcRn with IgGs selectively inhibiting IgGs rescue and recycling and inducing IgGs degradation and rapid clearance. In healthy volunteers, administration of efgartigimod reduced IgG levels up to 75% with IgG levels returning to baseline approximately 8 weeks following the last administration [31]. Efgartigimod was well tolerated and selectively reduced only circulating IgG. These results have been further supported in the first cohort of patients from a phase 2 trial in PV. In a phase 2 trial, six PV patients were treated with efgartigimod [33]. Disease control was reached in three out of six patients in 1 week whereas one patient reached disease control after 4 weeks. Two patients had progression of disease. Efgartigimod was well tolerated in all patients with no severe adverse events reported. FcRn inhibition can also be obtained with rozanolixizumab, a human FcRn mAb which determined sustained dose-dependent reductions in serum IgG concentrations in a randomized phase 1 study in healthy subjects [34].

In recent years, several studies have emphasized the important role of IgE autoantibodies in the pathogenesis of BP [35,36]. Consequently, a therapeutic approach using IgE depleting antibodies may represent a new option for treatment of this autoimmune disease. Omalizumab is a recombinant humanized mAb targeting the high-affinity receptor binding site on human IgE approved for treatment of moderate-to-severe IgE-mediated (allergic) asthma and chronic idiopathic urticaria [37]. Several reports indicate that BP patients can be treated successfully with omalizumab suggesting that this biological agent may be considered an alternative therapeutic option to immunosuppressive regimen, especially in patients with positive IgE anti-BP180 antibodies [38–40]. However, responses have been partial and, additionally, IgE antibody detection is not routinely available and therefore, it is currently not possible to determine which patient may not obtain adequate response. The mechanism of action of omalizumab is not completely understood in the treatment of BP. It has been demonstrated that BP180-specific IgE can sensitize mast cells and it is plausible that omalizumab prevents binding of IgE to its receptor inhibiting the activation of mast cells that are noted to be increased in skin lesions of BP [41]. To this regard, the pathogenicity of BP-180 IgE autoantibodies *in vivo* has been evaluated in mouse models, where injection of IgE purified from patients with BP into human skin transplanted onto nude mice reproduced the initial stage of disease development, notably mast cell activation and degranulation, eosinophil accumulation, and production of urticarial lesions [42]. Furthermore, binding of IgE antibodies obtained from sera of BP patients is observed on the surface of basal keratinocytes, leading to BP180 internalization, release of IL-6 and IL-8, and a reduction in the number of hemidesmosomes clear sign of skin rupture occurring at the level of the basement membrane zone [43]. Thereby blocking the binding of IgE antibodies to the surface of keratinocytes with omalizumab could interfere with this effector mechanism possibly leading to improvement in clinical symptoms. On the other hand, a subsequent investigation has demonstrated that surface bound IgG and not IgE determines eosinophil localization to basement membrane zone (BMZ) [44]. Larger trials are needed to better define the indication for omalizumab in BP and to determine the importance of measuring IgE anti-BP antigens in the management of BP.

Immunoadsorption is an apheresis procedure applied to remove total IgG from patient plasma using protein A or other ligands. In particular, it has been demonstrated in a mouse system that anti-Dsg3/1-specific autoantibodies adsorption may be a suitable therapeutic modality to

efficiently reduce pathogenic autoantibodies in patients with severe PV [45,46]. Consequently, specific removal of pathogenic autoantibodies would further increase efficacy and usability of immunoadsorption which in the future may replace conventional plasmapheresis (plasma-exchange), in the treatment of some autoimmune bullous skin conditions.

Intravenous immunoglobulin (IVIG) treatment is utilized to treat a wide range of autoimmune and inflammatory disorders including autoimmune bullous dermatoses. In particular, IVIGs may be given in PV as adjuvant (second- or third-line) therapy after failure of combined immunosuppressive treatment [47]. There are several possible mechanisms of action of IVIGs, notably neutralization of endogenous antibodies by anti-idiotype antibody production, Fc receptors modulation on phagocytes, B cells, and other cells, reduction in half-life of autoantibodies [48].

4. Targeting the complement system

Autoantibodies in BP have been suggested to activate the complement system leading to blister formation, whereas acantholysis in pemphigus has been demonstrated to be complement independent [49,50]. In all BP patients, basement membrane zone deposition of complement factor C3 has been found on direct immunofluorescence examination and, moreover, complement components and activation fragments including C1, C3, C3d, P, C5, and membrane attack complex (MAC) have been found at the basement membrane zone and blister fluid in BP implying that complement-dependent pathways are crucial in the immunopathogenesis of the clinical disease [51,52]. Subepidermal blistering is initiated by anti-BP 180 antibodies binding to the basement membrane zone but the mechanisms of blister induction by autoantibodies are not fully understood. Antigen–antibody complexes are thought to initially trigger the complement cascade which in turn may yield production of proteases and/or cytokines inducing dermal–epidermal separation [53]. Consequently, drugs targeting the complement cascade would be a logical approach to treat BP patients [54]. To this regard, eculizumab is a long-acting humanized mAb against complement C5 [55]. It blocks complement C5 cleavage, preventing the formation of C5a and C5b and the generation of C5a anaphylatoxin and formation of MAC. Eculizumab was initially registered for patients with paroxysmal nocturnal hemoglobinuria, where an acquired somatic mutation in the X-linked phosphatidylinositol glycan class A gene is responsible for complement-mediated hemolysis but it was associated with an increase in the risk of meningococcal disease [55]. Recently, it has also been used for the treatment of thrombotic thrombocytopenic purpura [55]. With regard to C1s blockade in humans, the experience using the humanized mAb IgG4 TNT009 is encouraging as it was reported to be safe and well tolerated in a first-in-human, double-blind, randomized phase 1 trial in 64 healthy volunteers [56]. Moreover, this antibody blocked complement activation by BP autoantibodies using an *ex vivo* human skin cryosection approach [57]. However, several lines of experimental evidence indicate that BP-IgG may be sufficient to induce skin fragility without complement activation; complements may only be required to induce inflammation and exacerbation of the disease [58–61]. Moreover, there is a predominance in BP of IgG4 antibodies which are not complement binding [50]. Also, dysfunction in BP180 (antibody independent) leads to phenotype similar to that of BP, which suggests a role of keratinocyte cellular signaling [62]. Consequently, these data should be taken into consideration with respect to the efficacy of complement inhibition as a potential therapeutic approach for BP and other autoimmune bullous dermatoses.

5. Targeting cytokines and chemokines

Increased levels of cytokines may contribute to the pathogenesis of several autoimmune conditions including bullous skin disorders. In the last decade, an increasing number of targeted anti-cytokine biological therapies have been developed but there are only few and hetereogeneous data with these options in autoimmune blistering conditions (Table 4).

In vitro and *in vivo* studies suggest that tumor necrosis factor (TNF)-alpha may have a role in PV pathogenesis [63–65]. Etanercept is a fully human recombinant fusion protein of the extracellular ligand-binding portion of the human 75-kDa TNF receptor and the Fc portion of human IgG1 that acts as a competitive inhibitor of TNF-alpha [66]. It is utilized for the treatment of several immuno-mediated diseases, including rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis [66]. A pilot study to evaluate the efficacy and safety of etanercept for PV therapy was carried out in six patients, but responses to etanercept were heterogeneous and the small sample size precluded definitive conclusions [67]. Infliximab is a human–mouse chimeric IgG1κ mAb composed of human constant and murine variable regions [68]. Infliximab binds specifically to human TNFα and is utilized for the treatment of various inflammatory disorders, such as adult Chron's disease, adult ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis [69]. Infliximab therapy was not shown to be effective for the treatment of patients with PV in a randomized, placebo-controlled trial, although this treatment determined a decrease in anti-DSG1 and DSG3 antibodies [70]. These data indicate that the utilization of an anti-TNF-alpha approach is not efficacious in this group of skin disorders. Furthermore, several cases of autoimmune bullous skin diseases occurring under anti-TNF-alpha therapy have been reported further indicating that this target therapy could not be an appropriate option for the treatment of these autoimmune skin conditions [71–73].

Recent data in human and mice indicate that Th17-cells may be involved in the pathogenesis of PV [74–76]. Ustekinumab is a biologic used for Crohn's disease, plaque psoriasis, and psoriatic arthritis [76]. It is a fully human IgG1α mAb which binds to the p40 subunit of IL-12 and IL-23 preventing these cytokines from binding to the IL-12β1 receptor on the surface of T cells [77]. Thus, ustekinumab blocks IL-12-induced Th1 cell activation and inhibits the secretion of pro-inflammatory cytokines (IL-2, TNFα, IFNγ) [77]. Ustekinumab also interferes with IL-23-induced Th17 cell effector function and the release of the pro-inflammatory cytokine IL-17 and consequently could be a rational approach for the treatment of PV [78]. However, lack of efficacy of ustekinumab in controlling pemphigus was

observed in a case indicating that the several cytokines blocked by this biological approach are probably not solely responsible for pemphigus pathogenesis [79].

The B-cell-stimulating molecules, BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand), are essential for the maintenance of the B cell pool and humoral immunity [80]. Moreover, BAFF and APRIL are supposed to be operative in the pathogenesis of several human autoimmune diseases, such as SLE, IgA nephropathy, Sjögren's syndrome, and rheumatoid arthritis [81]. These observations make both molecules potential targets for novel therapies in B-cell-mediated autoimmune diseases, including autoimmune blistering skin disorders. Several inhibitors of BAFF or BAFF and APRIL together have been investigated in clinical trials. These include the BAFF/APRIL dual inhibitor, atacicept, and the BAFF inhibitor, belimumab, which is approved as an add-on therapy for patients with active SLE [82,83]. However, serum levels of BAFF were not found to be elevated in patients with PV [84]. Furthermore, rituximab use in PV patients was found to lead to a significant elevation of serum BAFF levels but to a decrease in anti-DSG1 and anti-DSG3 autoantibody titers [85].

Epidermolysis bullosa acquisita (EBA) is a rare and chronic subepidermal autoimmune mucocutaneous bullous disease caused by autoantibodies directed against type VII collagen [2]. Several lines of evidence indicate that the role of cytokines in EBA is well established. In particular, it has been demonstrated that IL1b drives EBA [86] and blockades of TNF, GM-CSF, CXCR1/2, and IL17A have therapeutic effects in experimental EBA [87,88]. Furthermore, there is evidence that IL6 protects from induction of EBA through increased IL1ra expression whereas MIP1a is increased but does not contribute to EBA pathogenesis [89,90]. Consequently, these cytokines could be useful therapeutic targets for the treatment of this debilitating autoimmune bullous skin condition.

Bertilimumab is a fully human IgG4 mAb against eotaxin-1, an important regulator of eosinophil homing and migration into tissues [91]. There is evidence for a role of eosinophils in blister formation in bullous BP [92] and this has prompted the use of bertilimumab in BP. Clinical results from the BP-01 phase 2a study (clinicaltrials.gov identifier NCT02226146) showed that BP patients experienced substantial improvements in disease activity despite receiving only three doses of bertilimumab and a low dose of prednisone that was rapidly tapered [93]. FDA has granted Fast Track designation to bertilimumab for the treatment of BP.

IL-5 is involved in the differentiation, activation, and survival of eosinophils, whereas it has little, if any, effect on other lineages [94]. The production of IL-5 is associated with blood eosinophilia and significant eosinophil infiltration in the skin of BP patients [95]. Therefore, anti-IL-5 antibody therapy could be effective in depleting eosinophils in BP and controlled trials have been designed to determine the safety and efficacy of this approach in patients with BP [96,97].

6. Conclusions

In recent years, the number of biologic agents available to treat immunomediated diseases is expanding as a result of better understanding of the molecular mechanisms involved in the immunopathogenesis of these conditions. Several studies suggest that the use of biologics might also be beneficial for the treatment of several autoimmune blistering conditions including PV and BP. The promising therapeutic profile of these agents must be weighed against the cost of the medication and the risk of side effects indicating the need for controlled trials to assess efficacy and evaluate benefit/risk balance. Moreover, the use of biological agents in autoimmune blistering conditions should be individualized on the basis of severity of the disease, quality of life, and accurate assessment of comorbidities.

7. Expert opinion

Innovative strategies for the treatment of autoimmune blistering conditions primarily depend on the use of drugs with a high degree of specificity targeting crucial steps in the immunopathology of these disorders. Novel biological agents offer treatment alternatives to patients with autoimmune blistering conditions by targeting B cells, pathogenic autoantibodies, complement and cytokines.

Research efforts have made possible to obtain therapeutic approaches that can achieve depletion of circulating and resident B cells present in inflamed tissue and secondary lymphoid organs. Novel therapeutic strategies should be addressed to minimize B-cell dysfunction without affecting B cells which contribute to immune surveillance. At present, biological agents targeting B-cell surface markers are generally associated with diminished immunocompetence determined by the global B-cell depletion. Targeted approaches on autoantigen-specific B cell subsets are an attractive therapeutic alternative to complete B-cell elimination and will allow better patient management. To this regard, CAAR-T cell therapy could be a rational option against the autoantigen-specific B cell subsets involved in autoimmune blistering conditions [21]. This approach provides a highly specific targeted therapy that could obtain a permanent restoration of immune homeostasis in contrast to conventional biological treatment using mAb which are not able to permanently recover the self-tolerance state. In particular, this therapy has demonstrated to achieve in PV-specific depletion of self-reactive B cells, a decrease of circulating autoantibodies against DSG3, persistence of CAAR T-cells in circulation, and no cross-recognition with other tissues [21].

Therapy approaches based on lowering levels of pathogenic autoantibodies represent rational, effective, and safe treatment modalities of autoimmune diseases. Biological agents targeting pathogenic Ig autoantibodies have been exploited as novel approaches to treat some human autoimmune diseases. Targeting the neonatal Fc receptor for reducing pathogenic IgG autoantibodies is an attractive option for the treatment of autoimmune blistering conditions [23]. A pilot study in PV supports the use of this approach for the treatment of this condition. FcRn antagonism does not fully deplete IgG from serum decreasing the chance of hypogammaglobulinemia [24]. The absence of any demonstrable role in the suppression of antibody classes other than IgG also indicates that targeting FcRn may preserve immune system function and reduce the risk of severe infections. However, the safety and effectiveness of targeting

the FcRn in PV can only be assessed by large-scale clinical trials although these initial clinical findings support the viability of this therapeutic option.

At present, there are no definitive studies on the utilization of biological agents targeting complement and cytokines in autoimmune blistering conditions although these approaches could represent an appealing future therapeutic option. In particular, Th17 cells have emerged as attractive targets for therapies in autoimmune bullous skin conditions because of their propensity to generate inflammation to protect the body. In particular, IL-17A has been identified as an important regulatory molecule in BP [98] and innate immune cell-produced IL-17 was responsible for induction of inflammation in BP [99]. A number of biological agents targeting Th17-generated signaling molecules have been approved for the treatments of a wide range of autoimmune diseases, notably psoriasis, rheumatoid arthritis, multiple sclerosis, and Crohn's disease [100]. Clinical studies have demonstrated the effectiveness of these agents to act on the signaling involved in development of autoimmune diseases. While there are numerous active clinical trials related to PV, none of them are now investigating mAbs that target the Th17 pathway in this autoimmune condition. On the other hand, PV is a rare disease, with a long-term course and variable outcome, and thereby clinical trials that aim to assess the efficacy of biological agents in this disorder are difficult to design and/or perform. Consequently, international multicentric studies are necessary to evaluate the role of new biologics in the treatment of PV and the other autoimmune blistering disorders.

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