EXPERT OPINION ON INVESTIGATIONAL DRUGS
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REVIEW

Autoimmune blistering diseases: promising agents in clinical trials

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ABSTRACT

Introduction: Treatment options for autoimmune bullous diseases (AIBD) are currently limited to corticosteroids and traditional immunomodulants and immunosuppressants that are associated with unfavorable adverse effect profiles. The most frequent AIBDs, i.e. bullous pemphigoid, pemphigus vulgaris, and mucous membrane pemphigoid, impose a high disease burden onto affected patients and can be detrimental due to infections, exsiccosis, and impaired food intake. Significant progress has been made in elucidating disease mechanisms and key mediators by in vivo and in vitro models, thus identifying a multifaceted range of possible drug targets. However, except for rituximab for pemphigus vulgaris, no new drugs have been approved for the treatment of AIBDs in the last decades.

Areas covered: This review covers new drug developments and includes ongoing or completed phase 2 and 3 clinical trials. Studies were identified by querying the registries of ClinicalTrials.gov and Cochrane Library.

Expert opinion: Promising results were shown for a variety of new agents including nomacopan, efgartigimod, omalizumab, dupilumab, as well as chimeric autoantibody receptor T cells. Clinical translation in the field of AIBDs is highly active, and we anticipate significant advances in the treatment landscape.

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1. Introduction

The spectrum of autoimmune bullous diseases (AIBD) encompasses diseases characterized by intra- or subepidermal/-epithelial split formation caused by cellular and soluble effector mechanisms activated by autoantibody deposition in the epidermis or surface-close epithelia or along the dermoepidermal/-epithelial junction. Clinical features include blistering and erosions of skin or mucous membranes frequently accompanied by significant itch or pain [1–3]. As autoantibody targets and effector pathomechanisms are well characterized, a range of new treatment options has emerged in recent years [4].

The most frequent AIBD is bullous pemphigoid (BP) that has an incidence of approximately 10–20 per million but reaches 200–300 per million in ≥80-year-olds [5,6]. Risk factors are high age, certain medications (dipeptidyl peptidase IV-inhibitors, checkpoint inhibitors), neurological diseases, as well as specific HLA-haplotypes [7]. BP is characterized by tense blisters, erosions, urticarious or eczematous plaques, and severe itch. Blister formation can be preceded by a prebullous stage. Mucous membranes are affected in 10–30% of BP patients [3]. Due to infections and an increased risk for neurological conditions, such as Parkinson and Alzheimer's disease [8], a higher mortality of about 30% in the first year is observed in BP patients [9]. Histologically, subepidermal cleft formation as well as eosinophil-, lymphocyte-, and neutrophil-rich infiltrates are seen [10]. Linear deposits of predominantly IgG and complement C3 with an n-serrated pattern as well as more rarely IgE and IgA are found at the basement membrane by direct immunofluorescence (DIF). Antibody targets are mainly BP180 (type XVII collagen; immunodominant domain, NC16A) and/or BP230, two structural proteins of hemidesmosomes [11]. Disease severity is known to correlate with anti-BP180 serum levels [12]. Other rarer diseases within the pemphigoid group include linear IgA dermatosis, pemphigoid gestationis, anti-p200 pemphigoid, and epidermolysis bullosa acquisita. These diseases differ from each other in their clinical presentation, target antigen, autoantibody isotype, response to treatment, and prognosis. As such, exact diagnosis is essential also within the group of pemphigoid diseases [13].

Mucous membrane pemphigoid (MMP) is distinguished clinically from BP and other pemphigoid diseases by predominant affection of mucosae, while skin lesions are absent or mild [14]. Mono- or multisite disease can be found and typical localizations include the oral, ocular, genital or urological, tracheal, nasopharyngeal, and laryngeal mucosa besides skin [15]. Manifestations include erythema, erosions, ulcerations, and subsequent scarring; in particular, ocular MMP can induce symblephara, entropion, and trichiasis and often cause blindness. MMP is a rare disease affecting mainly the elderly with an incidence of 1–2 per million per year [5,6]. Pathomechanisms are heterogeneous. DIF can show linear deposits of IgG, IgA, IgM, and/or complement C3 at the basement membrane with an *n*-, u-, or undetermined serration pattern; however, initial DIF findings may be negative due to a low concentration of tissue-bound antibodies. The

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Article highlights

- Current therapy options in autoimmune bullous diseases are limited to corticosteroids, immunomodulants, such as dapsone and tetracyclines, immunosuppressants, IVIG, and rituximab. More efficient and safe options are urgently needed.
- Efgartigimod, an inhibitor of the neonatal Fc receptor, showed promising results in both pemphigus and pemphigoid diseases, and drug development is very advanced.
- Nomacopan, a dual inhibitor of complement C5a and leukotriene B_4, showed very encouraging preliminary results in BP patients, however, testing is halted. Complement inhibitors could provide a new therapy option in pemphigoid diseases.
- The anti-IL-4 receptor antibody dupilumab and benralizumab, an antibody against the IL-5 receptor, are currently explored in randomized controlled phase 3 studies in BP.
- In the next 5 years, licensing of efgartigimod for pemphigus and BP as well as for dupilumab and benralizumab in BP are anticipated if the current ongoing phase 3 studies can be evaluated positively.
- Unfortunately, for all other pemphigoid diseases, no new drug will be licensed in the next 5 years.

main target antigens are BP180 (mainly C-terminal epitopes) and laminin 332; BP230 and type VII collagen can also be recognized and individual patients with antibodies against α6β4 integrin have been described [16–21]. Laminin 332 autoantibodies are associated with neoplasms in about 25% of MMP patients [22–24].

Pemphigus diseases are characterized by intraepidermal cleft formation induced by autoantibodies against desmosomal structures. The main subtypes of pemphigus are pemphigus vulgaris (PV) and pemphigus foliaceus (PF); paraneoplastic pemphigus (PNP) and IgA pemphigus are extremely rare [1,2]. PV is the most frequent subtype at an incidence of 1–10 - per million per year with middle-aged persons affected most commonly [25]. It presents with painful erosions and ulcers of mucous membranes, mostly in the oral cavity, as well as flaccid blisters and erosions of the skin. PF exclusively involves the skin and shows puff-pastry-like scaling and erosions mainly in seborrheic areas, whilst PNP is characterized by severe mucositis affecting oral, ocular, anogenital, bronchopulmonary, and gastrointestinal mucosae besides skin [26]. DIF in PV, PF, and PNP shows intercellular deposits of IgG, complement C3 and more rarely IgA within the epidermis. Target antigens are desmoglein (Dsg)-3 and -1 in PV, Dsg-1 in PF and various desmosomal and plakin molecules in PNP including Dsg-1 and -3, desmocollins, envo-, peri-, and desmoplakin, plectin, BP230 [27–29] and α2-macroglobulin-like 1 protein [30].

2. Therapeutic landscape

The disease burden in patients with AIBDs is high due to intensely itchy or painful skin, mucous membrane lesions, subsequent infections, exsiccosis, impaired food intake, or breathing problems and can lead to substantial mortality if untreated. Current treatment strategies include systemic or topical glucocorticosteroids, immunomodulants, such as dapsone, tetracyclines, and intravenous immunoglobulins (IVIG), conventional immunosuppressants including azathioprine, mycophenoles, methotrexate, and cyclophosphamide (the latter only for severe ocular MMP) as well as rituximab [20,21,26,31–34].

In BP, a topical therapy with the superpotent corticosteroid clobetasol propionate is recommended at all stages. Systemic therapy is recommended for moderate and severe forms of BP and includes systemic corticosteroids with an initial dose of 0.5 mg/kg/day of prednisolone equivalent with or without adjuvant immunosuppressants/immunomodulants. The highest evidence has been provided for doxycycline and dapsone [35,36] but also azathioprine, mycophenolate mofetil, mycophenolic acid, or methotrexate are recommended. Options for treatment-resistant cases are IVIG (2 g/kg/cycle, cycles every 4 weeks), immunoadsorption, and rituximab (two administrations of 1 g at day 0 and day 14–21) [33,34]. Especially in elderly patients, high corticosteroid doses and immunosuppression can be accompanied by a high frequency of adverse events. Mortality in patients with BP correlates with high corticosteroid doses [37]. Relapses were reported in around 30% of patients and correlated with initial disease extend and concomitant dementia [38].

Most patients with MMP require systemic therapy unless in mild oral or ocular disease. Moderate cases are treated with systemic steroids (0.5–1 mg/kg/day prednisolone) and/or adjuvant dapsone or doxycycline and alternatively mycophenolate, methotrexate, or azathioprine. Severe cases require higher corticosteroid doses and can additionally be treated with cyclophosphamide (in severe ocular diseases), a combination of adjuvant immunosuppressants or -modulators, IVIG, or rituximab. Topical therapies include corticosteroids and calcineurin inhibitors (ointments, cremes or eye drops). For ocular MMP, serum eye drops can be used for severe dryness; further, surgical procedures can be recommended (including amniotic membrane or corneal stem cell grafts and keratoprosthesis) [20,21,32].

Pemphigus diseases are treated systemically unless the disease is clinically very limited. Initial therapy for mild pemphigus includes systemic steroids (1–1.5 mg/kg/day prednisolone) and adjuvant azathioprine, mycophenolate or, only for PF, dapsone. With this regimen, about 20–30% of patients achieve complete remission [39]. Alternatively, rituximab can be given. Severe disease is preferentially treated with rituximab as the first-line treatment, initially combined with systemic corticosteroids and possibly immunosuppressants. In this approach, about 25% of pemphigus patients will suffer from a relapse and 40% from severe adverse events [40]. Refractory cases can receive higher corticosteroid doses, adjuvant immunoadsorption, or IVIG. In all stages, antiseptic measures are recommended and topical corticosteroids or calcineurin inhibitors can be given [26,31,33].

In summary, patients with AIBDs are in high need for more efficient therapies and are susceptible to adverse effects of strong immunosuppression due to patient demographics and comorbidities. Thus, novel therapies are needed to amend the arsenal of therapy options that is currently mostly limited to steroids and traditional immunosuppressants.

3. New drugs in clinical trials

We queried the clinical trial registries of ClinicalTrials.gov and Cochrane Library in April 2023 for the terms ('pemphigus' OR

Table 1. Ongoing randomized controlled trials in autoimmune blistering diseases.

Indication	Investigational compound	Mechanism of action	Design	Status
BP	Dupilumab	Anti-IL-4 R	RCT, Phase 3	recruiting
BP	Avdoralimab	Anti-C5aR1	RCT, Phase 2	recruiting
BP	Efgartigimod	Anti-FcRn	RCT, Phase 2/3	recruiting
BP	Benralizumab	Anti-IL-5 Rα	RCT, Phase 3	recruiting
MMP	Rituximab	Anti-CD20	RCT, Phase 3	recruiting
oc. MMP	Baricitinib	JAK1/2-inhibitor	RCT, Phase 2	recruiting
PV/PF	Efgartigimod	Anti-FcRn	RCT, Phase 3	active
PV/PF	Efgartigimod	Anti-FcRn	RCT, Phase 3	recruiting
PV	Abatacept	Anti-CD52	RCT, Phase 4	recruiting

Note: BP, bullous pemphigoid; IL, interleukin; FcRn, neonatal Fc receptor; JAK, janus kinase; MMP, mucous membrane pemphigoid; oc., ocular; PF, pemphigus foliaceus; PV, pemphigus vulgaris; RCT, randomized controlled trial.

'pemphigoid' OR 'autoimmune bullous disease') and found records of 49 registered trials after screening titles and abstracts and excluding duplicates, studies in unrelated diseases and studies with already approved interventions. Of those, nine-phase 2/3 randomized controlled trials (RTC) are currently being performed (Table 1). Identified drug targets were involved in processes of autoantibody production (Figure 1a), autoantibody processing and trafficking (Figure 1b), or soluble and cellular actors of the effector phase (Figure 1c).

3.1. Inhibitors of the neonatal Fc receptor (FcRn)

The neonatal Fc receptor (FcRn) is a major histocompatibility class 1-like molecule involved in recycling of IgG-molecules. FcRns enhance the half-life of pathogenic autoantibodies in patients with AIBDs by binding Fcγ-portions and thereby protecting IgG-molecules from lysosomal degradation [41]. Also, direct effects of FcRns on keratinocyte adhesion and autoantibody production were proposed [42,43]. The clinical efficacy of IVIG is mainly attributed to the blockade of FcRns by a saturation with IgG leading to decreased stability of endogenous pathogenic IgG-molecules in pemphigoid or pemphigus patients [44] (Figure 1b).

Efgartigimod is an engineered Fc-fragment derived from human IgG1 that antagonizes FcRns and was approved for myasthenia gravis, another autoantibody mediated disease, in 2021 by the U.S. Food and Drug Administration (FDA) and in 2022 by the European Medicines Agency (EMA). A completed phase 2 trial showed early disease control in 90% of patients with PV or PF within 7 days as well as complete remissions in 64% within 41 weeks, while patients continued systemic corticosteroids (NCT03334058) [45]. Concordantly, serum levels of anti-Dsg-1 or -3 as well as frequencies of Dsg-1- or -3-reactive B cells dropped under therapy with efgartigimod; after discontinuation, those interestingly remained low, while total IgG and virus-specific IgG concentrations were normal [43]. The ADDRESS randomized double-blind controlled phase 3 study for patients with PV or PF is currently active and completed recruitment (NCT04598451); the follow-up study ADDRESS+ is recruiting (NCT04598477).

For BP, the randomized double-blind placebo-controlled combined phase 2 and 3 study BALLAD (NCT05267600) testing efgartigimod is currently recruiting, and a follow-up study BALLAD+ is registered (NCT05681481).

The anti-FcRn IgG4 humanized antibody Orilanolimab (SYNT001) may be trialed in the future after successful dose-finding studies (NCT03075904) [46].

3.2. Inhibitors of the complement system

In pemphigoid diseases, complement proteins fixed by pathogenic skin-bound IgG4 antibodies as well as soluble-activated complement factors play an important role in initiating and sustaining cellular responses of the effector phase, foremostly by chemotaxis and activation of neutrophils via the C5a receptor 1 (C5aR1). In addition, engagement with complement factors induces secretion of the leukotriene B_4 (LTB_4) from neutrophils further perpetuating the effector cellular response in an auto-/paracrine manner (Figure 1c) [47,48]. Nomacopan is a recombinant protein initially isolated from the soft tick *Ornithodoros moubata* that dually blocks C5a and LTB_4. An uncontrolled phase 2 study in BP patients not using systemic corticosteroids during and 5 days before the study showed clinical responses in 78%, and 33% reached complete remissions under a monotherapy with nomacopan (NCT04035733) [49]. The planned randomized double-blind controlled phase 3 study ARREST-BP with nomacopan for BP patients is currently halted by the funder currently prioritizing other indications (NCT05061771).

The monoclonal antibody avdoralimab blocks C5a signaling exclusively via binding to C5aR1, while the potentially pro-resolving and protective C5aR2 signaling remains unaffected. A phase 2 case-controlled trial is currently recruiting (NCT04563923).

3.3. Inhibitors of T helper 2 cell (Th2)-/IgE-mediated responses

BP is known to feature increased serum levels of interleukin (IL)-4, -13, and other T helper 2 cell (Th2)-associated cytokines as well as their detection in blister fluid, increased total IgE, peripheral eosinophilia, and degranulation of mast cells and basophils in urticarial lesions (Figure 1c). Hence, several inhibitors developed for other Th2-mediated diseases are being tested in BP.

Dupilumab, an inhibitor of IL-4 and -13 signaling, showed clinical efficacy in BP in retrospective cohort studies and led to quicker disease control, reduction of itch and skin lesions. Remission rates of 86–92% were reported after 6 months of treatment [50], including a recent large retrospective study

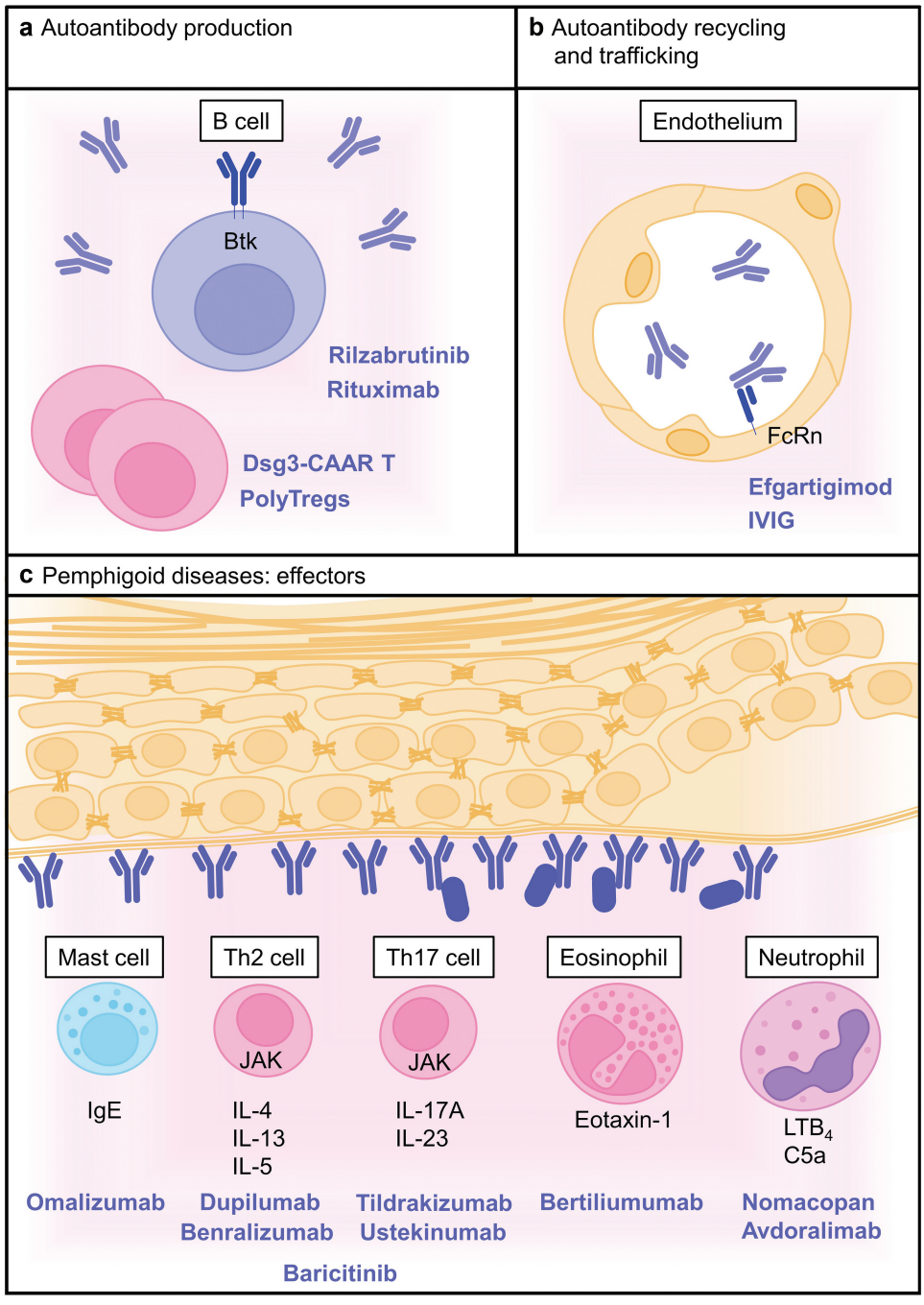

Figure 1. Specific targets of selected drugs approved for AIBDs or currently in phase 1, 2 or 3 clinical studies. (a) Autoantibody production by B cells in AIBDs is crucial for disease initiation; inhibitors of Bruton's tyrosine kinase (Btk) that plays a role in the B cell receptor signaling, and cellular blockers of B cell activation are in testing, including Dsg3-chimeric autoantigen receptor T (CAAR T) cells and polyclonal regulatory T cells (PolyTregs) for PV. (b) Autoantibodies are recycled by neonatal Fc receptors (FcRn) expressed primarily on endothelia which leads to prolonged plasma half-life. Inhibitors of FcRn are in testing for both pemphigus and BP. (c) Cellular and soluble effectors in pemphigoid diseases include mast cells/basophils, type 2 and type 17 helper T cells (Th2; Th17), eosinophil and neutrophil granulocytes, complement factors fixated and activated by deposited autoantibodies as well as various cytokines. Janus kinases (JAK) play a role for the intracellular signaling of multiple cytokines in particular for T helper cells.

with 36 patients [51]. Currently, the placebo-controlled phase 3 trial LIBERTY-BP (NCT04206553) is recruiting [52].

Further, inhibitors of eosinophil-activating cytokines were used for patients with BP: benralizumab, an antibody against the IL-5 receptor, is currently being tested in the phase 3 randomized controlled FJORD study (NCT04612790). In contrast, mepolizumab, an IL-5 inhibitor, showed no effect in BP in a previous randomized controlled phase 2 study. Here, 20 patients were treated with 750 mg mepolizumab every 4 weeks over 12 weeks and additional 0.5 mg/kg prednisolone which was tapered after cessation of new blister formation. Disease scores, corticosteroid use, itch rating, and serum autoantibody levels did not differ between the treatment groups; however, mepolizumab led to reduced peripheral eosinophil counts [53].

Bertilimumab, an eotaxin-1 inhibitor, was tested in a phase 2 interventional trial that has not posted results yet

(NCT02226146). An oral inhibitor of CCR3 was tested in a phase 2 trial with no published results (NCT04499235); contrarily, an oral inhibitor of CXCL-8 proved ineffective in a phase 2 trial (NCT01571895).

Anti-IgE antibodies were used in BP based on the finding of anti-BP180 and anti-BP230 IgE-antibodies in about 50% of BP patients possibly inducing mast cell and basophil degranulation as well as a correlation of total IgE-levels with disease severity [54]. Omalizumab led to rapid amelioration of pruritus in case series of patients with BP or pemphigoid gestationis and reduced disease severity [55,56]. A phase 2 clinical trial evaluating omalizumab in combination with rituximab is registered but not yet recruiting (NCT04128176); clinical data is currently limited by low case numbers. Similarly, ligelizumab was tested in a phase 2 trial but failed to demonstrate efficacy (NCT01688882).

3.4. Inhibitors of T helper 1 cell (Th1)- and Th17-mediated responses

Besides type 2-inflammation, upregulation of Th1 and Th17-related cytokines and associated genes has been found in lesional skin in BP [57]; especially IL-17A was identified as a key driver of BP (Figure 1c). However, in a small phase 2 uncontrolled study with the anti-IL-17A antibody ixekizumab, all enrolled patients discontinued the treatment due to a lack of efficacy (NCT03099538). Currently, the open-label phase 2 trial PB-USTE with the IL-12 and -23 inhibitor ustekinumab (NCT04117932) and a phase one trial with the IL-23 inhibitor tildrakizumab are in preparation (NCT04465292). Extracts from *Tripterygium wilfordii* are known to inhibit Th17 – as well as TNFα mediated Th1-skewed immune responses, and a small retrospective study found a ≥ 90% reduction of involved skin area in 7/10 patients with BP treated in monotherapy [58]. In ocular MMP, notably, the TNFα-release inhibitor pentoxifylline showed significant improvement of clinical parameters including cicatrization in a small controlled phase 2 study [59].

In pemphigus, Th1-related cytokines such as TNFα and IFNγ were found in higher concentrations in patient sera [60]. Two previous small phase 2 studies, however, found no differences in patients with PV treated with the TNFα-inhibitors infliximab [61] or etanercept [62] compared to placebo-treated groups.

3.5. Kinase inhibitors

Bruton's kinase (Btk) is involved in the signal transduction of the B cell receptor, and Btk-inhibitors are in clinical use for B cell malignancies. As pemphigus diseases are autoantibody-mediated, Btk-inhibitors were used in pemphigus patients with the rationale of abrogating pathogenic B cell responses (Figure 1a). The highly specific Btk inhibitor rilzabrutinib was tested in the open-label phase 2 trial BELIEVE and showed disease control with a concomitant corticosteroid dose of less than 0.5 mg/kg/day in 60% of patients with PV after 4 weeks and complete remissions in 33.3% after 24 weeks as well as significant decreases of anti-Dsg-3 titers [63,64]. The phase 3 trial PEGASUS, however, was terminated due to a lack of statistical significance in an interim analysis; preliminary data showed complete remissions in 30 of patients treated with rilzabrutinib versus 18% of the placebo group at weeks 29–37 with a corticosteroid dose of less than 10 mg/kg/day ($p = 0.4469$) as well as a longer duration of complete remissions (NCT03762265).

Other kinase inhibitors tested for PV in phase 2 studies are the Abl inhibitor imatinib (university hospital medical information network registry no. UMIN000030865), the mammalian target of rapamycin (mTOR)-inhibitor sirolimus (NCT01313923), and the p38-mitogen activated kinase inhibitor KC706 (NCT00606749); results were, however, not published. A study investigating parsaclisib, an inhibitor of phosphoinositol-3-kinase delta (PI3Kδ) (NCT03780166) was withdrawn.

In MMP, case reports showed positive effects of Janus kinase (JAK) inhibitors [65,66]. A phase 2 trial for the JAK1/2-inhibitor baricitinib comparing with a methotrexate-treated control group is currently recruiting patients with ocular MMP (NCT05263505).

3.6. B cell-directed therapies

The B cell depleting antibody rituximab is approved for the first-line treatment of pemphigus vulgaris, and based on clinical data, it is recommended as an off-label treatment of recalcitrant BP or MMP as well as pemphigus foliaceus. Currently, the phase 3 controlled trial RITUX-MMP is comparing rituximab versus cyclophosphamide in patients with MMP (NCT03295383).

Similar to rituximab, other B cell depleting antibodies were explored in PV in phase 2/3 studies including the B cell activating factor (BAFF) receptor antibody ianalumab (NCT01930175) and the CD20 antibody ofatumumab (NCT01920477, NCT02613910). Development was subsequently discontinued after the approval of rituximab.

Instead of unselective B cell depletion, a strategy for targeted killing of Dsg-3 reactive B cells was pursued by adapting the chimeric antigen receptor (CAR) T cell technology (Figure 1a): Chimeric autoantigen receptor (CAAR) T cells are genetically engineered patient T cells with a transgene mediating cytotoxic T cell effects upon engagement with anti-Dsg -3 B cell receptors. Dsg-3-CAAR T cells showed reduction of anti-Dsg-3 titers and disease severity in preclinical PV-models [67]. A phase 1 open-label dose finding trial is currently recruiting patients with PV (NCT04422912).

3.7. T cell-directed therapies

Another strategy of inhibiting autoreactive B cell and T cell responses is via regulatory T cells (Tregs). A phase 1 trial showed the safety of polyclonal Treg transfusions in patients with pemphigus but was discontinued due to feasibility issues (NCT03239470). An ongoing phase 1 trial is testing Dsg-3-peptides coupled with nanoparticles (TPM203) that are hypothesized to induce a Dsg-3-specific Treg response and hence downregulate pathogenic anti-Dsg-3 T cell and B cell responses (EU clinical trials register EudraCT-2019–001727–12).

3.8. Immunoadsorption

Serum levels of autoantibodies can be efficiently reduced by immunoadsorption with protein A in a technique resembling dialysis [68–70]. In pemphigus, the phase 3 RTC *IA-pem*

(German clinical trials register DRKS00000566) with 72 patients compared best medical treatment, i.e. prednisolone at an initial dose of 1.0 mg/kg/day with best treatment plus immunoadsorption. The trial showed a shorter time to remission in patients with severe disease and a significantly lower cumulative corticosteroid dose in the immunoadsorption arm. However, the primary endpoint, time to remission in all included patients, was not significantly different between the two treatment arms. In addition, severe adverse events were reported in both groups [71]

In severe or refractory bullous pemphigoid, a yet unpublished pilot study with 10 patients showed remissions in 90% of patients after 6 months with an 85% decrease of the initial anti-BP180 serum IgG levels after three immunoadsorptions on consecutive days combined with standard treatment. Standard treatment comprised prednisolone (tapering doses of 0.5 mg/kg/day) combined with dapsone (1.5 mg/kg/day) and mometasone furoate ointment (lesional, twice daily) [72].

3.9. Other therapy strategies

Other ongoing clinical trials include the interventional trial ARABUL testing the fusion protein abatacept that inhibits CD28-mediated T cell responses in patients with PV (NCT05303272) and the phase 2 open label trial CELOPHIN testing transplantation of mesenchymal stem cells (MSC) locally in patients with ocular MMP (NCT05520086). A phase 3 RTC in BP compared methotrexate combined with clobetasol propionate ointment with the ointment alone but has not posted results yet (NCT02313870). A small phase 2 trial demonstrated the feasibility of metabolic intervention with metformin in patients with PV [73] finding reduced total serum IgG4 and lower concentrations of proinflammatory cytokines. A similar strategy could be hypothesized for pemphigoid diseases based on preclinical data [74].

Strategies that proved ineffective for the treatment of AIBDs in phase 2 clinical trials or were not investigated further are a vaccination with synthetic Dsg-3 peptides (NCT00063752) and acyclovir treatment [75] in PV, as well as IL-2 (Chinese clinical trial registry ChiCTR2000028707), phosphodiesterase (PDE)-4 inhibitors (Japan registry of clinical trials jRCT2071210034), leflunomide (NCT00802243), and the plant-based Jingui Shenqi pill modulating glucocorticoid receptors [76] in BP.

4. Conclusion

In summary, a variety of targeted therapies for AIBDs are in clinical testing. Promising preliminary results were shown for the FcRn-inhibitor efgartigimod in pemphigus and BP with randomized controlled trials for both indications being in progress. CAAR T cells could show efficacy and tolerable safety in patients with severe PV. The spectrum of treatment options for BP could be broadened by dupilumab, nomacopan and benralizumab. Further, JAK-inhibitors are the most promising drugs for testing in MMP.

5. Expert opinion

5.1. Pemphigus diseases

With the positive phase 2 data and the imminent publication of phase 3 results, the neonatal Fc-receptor inhibitor efgartigimod is a potential candidate for expected approval in the near future for pemphigus diseases. A significant advantage over the current standard therapy with rituximab is the constant serum IgG levels and preserved antibody titers against viral targets found with efgartigimod. Anti-CD20 therapy contrarily leads to global suppression of the adaptive B cell immunity that can be detrimental, especially in infection-prone pemphigus patients.

Even though the Btk inhibitor rilzabrutinib failed to demonstrate significant advantages in the recent phase 3 trial, one must acknowledge the high corticosteroid doses concomitantly used in both treatment and control groups and the very heterogeneous cohort. Btk inhibitors might prove beneficial in AIBDs in the future, considering the more promising data in other autoantibody-mediated diseases such as in immune thrombocytopenia and a relatively safe adverse effect profile [77]. The notion that autoantibody-producing plasma cells do not depend on Btk signaling and are thus unavailable to therapy with Btk inhibitors is contrasted by the efficacy of anti-CD20 therapy despite low CD20-expression on plasma cells.

CAAR T cells could be a promising therapy option for very severe cases of PV. However, while production and clinical management of CAR T cell therapies is well established in specialized centers, high cost, and potentially severe side effects must be considered, including strong immune suppression during the pre-treatment T cell depleting chemotherapy, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). Also, Dsg-1 autoantibodies that can play an important role in PV are mechanistically expected to be unaffected by Dsg-3 CAARs. The vaccination approach with Dsg-3-specific nanoparticles may lead to robust reduction of anti-Dsg-3 T cell responses. On the other hand, it remains unclear how this method can function in severe PV when strong immunosuppressants are required.

5.2. Bullous pemphigoid

Efgartigimod is in clinical testing for BP, in parallel with pemphigus diseases. However, the trials in BP are currently not as advanced as in pemphigus diseases and the data are still limited. Preclinical data showing a high relevance of FcRn in BP-models [78], as well as mechanistic overlaps with IVIG, might suggest possible positive effects.

Inhibitors of the complement system are a promising drug class in BP, especially considering the very positive effects of nomacopan monotherapy in the recent phase 2a trial and the relatively good drug safety. Further testing is still needed but momentarily paused.

Clinical data on omalizumab showed good anecdotal evidence, especially in acute and urticarial BP; however, no larger phase 2 or phase 3 trials are currently active. Anti-IgE

therapy could provide an option for quick symptom relief in frail patients with contraindications to strong immunosuppression but could be associated with a high chance of relapse.

Similarly, dupilumab demonstrated efficient symptom control as an add-on- or monotherapy in several BP cases and could evolve into a treatment alternative for patients with neoplasms or other severe underlying diseases. Data from the recent phase 3 study LIBERTY-BP are highly anticipated.

5.3. Mucous membrane pemphigoid

In MMP, unfortunately, the spectrum of ongoing therapeutic interventions is very limited. The only RTC is currently exploring the efficacy and safety of rituximab versus cyclophosphamide in MMP. Case reports showed the effects of the JAK-inhibitors baricitinib and tofacitinib, and a phase 2 trial with baricitinib is currently recruiting. Other interventions in clinical testing are focused on symptom control.

5.4. Other autoimmune blistering diseases

Due to their rarity, no RTC is currently performed in other autoimmune bullous diseases to the best of our knowledge.

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Declaration of interest

ES has research cooperations with UCB, Incyte, Biotest, ArgneX, Dompe, Admirx, Biondis, Fresenius Medical Care, Pharmaxis, Alpine Immune, Bayer, CSL, AstraZeneca, and Pincell. ES received honoraria or travel grants from Biotest, ArgenX, Sanofi, Fresenius Medical Care, AstraZeneca, Leo, Chugai, Sanofi, and Almirall. CDS co-filed a pending patent on the use of nomacopan for bullous pemphigoid. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Author contributions

HO drafted the manuscript. CDS and ES revised the manuscript. All authors approved the submitted version.

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