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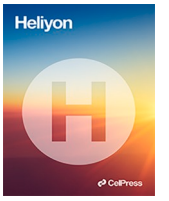

Review article

Targeting therapy in pemphigus: Where are we now and where are we going?

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ABSTRACT

Pemphigus is a heterogeneous group of autoimmune skin disorders characterized by blistering of the skin and mucosal membranes, potentially affecting the quality of life if left unchecked. The current mainstay of treatment is systemic corticosteroids and immunosuppressive agents. Nevertheless, long-term use of these drugs can easily cause infections and other life-threatening adverse reactions. Thus, currently, researchers are trying to develop new and safer therapeutic approaches. Specifically, targeted therapies to pathogenic immune pathways have been gradually introduced and used for the treatment of pemphigus or in clinical trials, such as monoclonal anti-CD20 antibody, BAFF inhibitor, BTK inhibitor, CAAR-T therapy, FcRn antagonist, and TNF-α inhibitor. In addition, IL-4Rα antibody, IL-17 blockade, mTOR pathway inhibitor, CTLA-4Ig, and p38 MAPK inhibitors are theoretically promising treatment for pemphigus. Here, we review the research progress on the mechanism of targeted therapies for pemphigus.

1. Introduction

Pemphigus diseases are a group of autoimmune blistering diseases affecting the skin and mucous membranes [1]. The main clinical manifestations of pemphigus are intra-epidermal blistering and flaccid blisters, caused by the loss of cell-cell adhesion due to auto-antibodies against cell adhesion proteins desmogleins 1 (Dsg1) and desmogleins 3 (Dsg3) [2]. Pemphigus diseases include pemphigus vulgaris (PV), pemphigus foliaceus (PF), pemphigus vegetans, pemphigus erythematosus, pemphigus herpetiformis, paraneoplastic pemphigus (PNP), IgA pemphigus, and drug-induced pemphigus [2]. PV is the most common and severe form of pemphigus, mediated by *anti*-Dsg1 and *anti*-Dsg3, affecting oral mucosa and skin [1]. Painful oral lesions are usually the first manifestation. Compared to PV, PF is mainly mediated by *anti*-Dsg1 and only affects the skin [3]. Due to the defects in the skin barrier, leakage of exudate onto the skin surface can easily attract bacteria to multiply on-site, with subsequent skin infections that may threaten the life of patients [2]. The diagnosis of pemphigus requires clinical presentation and histopathology consistent with pemphigus and a positive direct immunofluorescence (DIF) microscopy or serologic detection of autoantibodies against epithelial cell surface antigens [3]. The Pemphigus Disease Area Index (PDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) are the usual scoring systems used to evaluate the extent and activity of pemphigus [3]. Since the advent of glucocorticoid (CS) therapy for the treatment of pemphigus in 1950, the prognosis of pemphigus has largely and rapidly improved. Afterward, using CS alone or combined with immunosuppressive

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agents is the main treatment for pemphigus [4]. Despite controlling the disease, long-term high-dose CS therapy inevitably causes some adverse reactions, such as headaches, insomnia, obesity, fluid retention, osteoporosis, cardiovascular diseases, type 2 diabetes mellitus, and insulin resistance [5]. During the past few decades, treatment methods have been tremendously updated based on a better understanding of the pathogenesis. In this study, we review the recent advances in the mechanism of targeted therapy for pemphigus. According to our current understanding of pemphigus pathogenesis, we classified the emerging targeted therapy into five

Table 1
Clinical trials of targeted therapy for pemphigus with updated data in the last 5 years.

Interventions	Study Title	Study Results	Phases	Start Date	Last Update Posted	URL
Drug: Abatacept Prefilled Syringe	A Study to Evaluate Efficacy and Safety of Abatacept in Participants of Pemphigus Vulgaris (PV)	NO	PHASE4	2021/2/1	2022/3/31	https://ClinicalTrials.gov/show/NCT05303272
Biological: efgartigimod PH20	A Study to Assess the Long-term Safety and Efficacy of a Subcutaneous Formulation of Efgartigimod PH20 SC in Adults With Pemphigus (Vulgaris or Foliaceus)	NO	PHASE3	2021/7/15	2023/2/28	https://ClinicalTrials.gov/show/NCT04598477
Biological: efgartigimod PH20	A Study to Assess the Efficacy and Safety of a Subcutaneous Formulation of Efgartigimod PH20 SC in Adults With Pemphigus (Vulgaris or Foliaceus)	NO	PHASE3	2020/12/1	2023/2/28	https://ClinicalTrials.gov/show/NCT04598451
Biological: DSG3-CAART	Open-label Study to Determine the Maximum Tolerated Dose of DSG3-CAART in Mucosal-dominant PV Patients (mPV)	NO	PHASE1	2020/9/29	2022/12/2	https://ClinicalTrials.gov/show/NCT04422912
Drug: Rituximab	IVIG With Rituximab vs Rituximab as First Line Treatment of Pemphigus	NO	PHASE2	2020/6/20	2022/10/21	https://ClinicalTrials.gov/show/NCT04400994
Drug: Rituximab	Clinical and Immunological Long-term Follow-up of Patients With Pemphigus Included in the "RITUXIMAB 3″ Trial	NO	PHASE3	2019/12/1	2018/12/31	https://ClinicalTrials.gov/show/NCT03790293
Drug: Parsaclisib	A Study of the Safety and Tolerability of INCB050465 in Pemphigus Vulgaris	NO	PHASE2	2019/3/1	2019/9/13	https://ClinicalTrials.gov/show/NCT03780166
Drug: Rilzabrutinib	A Study of PRN1008 in Patients With Pemphigus	YES	PHASE3	2019/1/8	2022/9/21	https://ClinicalTrials.gov/show/NCT03762265
Drug: ARGX-113	A Study to Evaluate the Safety, PD, PK and Efficacy of ARGX-113 in Patients With Pemphigus	NO	PHASE2	2017/10/18	2020/12/14	https://ClinicalTrials.gov/show/NCT03334058
Biological: Cohort PolyTregs	Polyclonal Regulatory T Cells (PolyTregs) for Pemphigus	YES	PHASE1	2017/10/10	2023/2/14	https://ClinicalTrials.gov/show/NCT03239470
Drug: ALXN1830	A Safety and Dose-Finding Study of SYNT001 in Subjects With Pemphigus (Vulgaris or Foliaceus)	YES	PHASE1/2	2017/7/18	2020/2/5	https://ClinicalTrials.gov/show/NCT03075904
Drug: PRN1008	A Study of PRN1008 in Adult Patients With Pemphigus Vulgaris	YES	PHASE2	2016/1/22	2023/2/13	https://ClinicalTrials.gov/show/NCT02704429
Drug: Ofatumumab	Long-Term Extension Study of Ofatumumab in Subjects With Pemphigus Vulgaris	YES	PHASE3	2015/12/23	2017/6/14	https://ClinicalTrials.gov/show/NCT02613910
Drug: Rituximab	A Study to Evaluate the Efficacy and Safety of Rituximab Versus Mycophenolate Mofetil (MMF) in Participants With Pemphigus Vulgaris (PV)	YES	PHASE3	2015/5/26	2020/11/10	https://ClinicalTrials.gov/show/NCT02383589
Drug: VAY736	Study of Efficacy and Safety of VAY736 in Patients With Pemphigus Vulgaris	YES	PHASE2	2013/12/18	2021/10/8	https://ClinicalTrials.gov/show/NCT01930175
Biological: Ofatumumab	Efficacy and Safety of Ofatumumab in Treatment of Pemphigus Vulgaris	YES	PHASE3	2013/8/13	2019/6/6	https://ClinicalTrials.gov/show/NCT01920477
Drug: Sirolimus (Rapamycin)	Evaluating Sirolimus to Treat Autoimmune Blistering Dermatosis Pemphigus	YES	PHASE1	2011/2/1	2017/6/9	https://ClinicalTrials.gov/show/NCT01313923
Drug: Rituximab	Comparison Between Rituximab Treatment and General Corticotherapy Treatment in Patients With Pemphigus	NO	PHASE3	2009/7/1	2017/6/14	https://ClinicalTrials.gov/show/NCT00784589
Drug:Rituximab	Immunoadsorption, Dexamethasone Pulse Therapy and Rituximab for Pemphigus	YES	PHASE2	2008/1/1	2017/3/13	https://ClinicalTrials.gov/show/NCT00656656
Drug: Infliximab	Use of Infliximab for the Treatment of Pemphigus Vulgaris	YES	PHASE2	2006/3/1	2017/12/6	https://ClinicalTrials.gov/show/NCT00283712

categories: (1) modulation of B cell function; (2) modulation of autoantibody (IgG) half-life; (3) inhibition of inflammatory markers; (4) immunological checkpoint receptors agonists; (5) inhibition of the blister-inducing activity of autoantibodies (Table 1).

2. Modulation of B cell function

2.1. Monoclonal Anti-CD20 antibody

CD20 (Cluster of Differentiation 20) molecule is a B-lymphocyte membrane protein expressed on the surfaces of early B cells (including pre-B cells, immature B cells, and mature B cells) [6]. In addition, CD20 plays a critical role in the growth and differentiation of B cells [7]. CD20 molecule is a phosphoprotein of 297 amino acids with four transmembrane domains 8. The CD20 molecule includes two extracellular loops (a large loop and a small loop), and its extracellular portion is 44 amino acids in length [6]. The two extracellular loops are epitope binding sites for the anti-CD20 monoclonal antibody (MAb) [8]. Human CD20 is encoded by the gene MS4A1 located on chromosome 11q12.2 [9]. It functions by binding to Src family tyrosine kinases, such as Lyn, Fyn, and Lck, and is believed to be involved in the phosphorylation cascade of intracellular proteins [10]. B-lymphocytes play a role as potent antigen-presenting cells in autoimmune diseases [10]. In human beings, anti-CD20 MAb selectively removes B-lymphocytes from the blood, lymph nodes, and bone marrow [6]. As CD20 molecules are not expressed on pro-B cells and plasma cells, the number of circulating B cells in the body can still be replenished through maturation despite prior treatment with anti-CD20 MAb while maintaining protection from previous vaccinations and infections [6].

2.1.1. Rituximab, RTX

RTX is a mouse-human chimeric anti-CD20 immunoglobulin (Ig)G1 monoclonal antibody [8]. Its epitope binding site is near the extracellular loop of CD20. Antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are the main mechanisms for attacking CD20-positive B cells of RTX [10, [11]. As a result, circulating *anti*-Dsg1/3 autoantibodies can be rapidly and significantly reduced, in which the remission state can be maintained for at least 6–12 months, improving the general condition of pemphigus patients [12]. RTX was first introduced in the treatment of PNP and PV in 2001 and 2002, respectively [5]. In 2014, Japanese guidelines for managing pemphigus recommended using RTX in cases of severe pemphigus, which are resistant to conventional treatment modalities (such as CS and immunosuppressant therapies) [2]. Other guidelines from the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV) suggested RTX as third-line adjuvant therapy for refractory pemphigus or cases where immunosuppressants are contraindicated [13]. In 2017, a prospective randomized controlled trial involving 90 patients by Joly et al. demonstrated that RTX combined with short-term prednisone is more effective than using prednisone alone for newly diagnosed pemphigus [12]. The guidelines by the British Association of Dermatologists (BAD) suggested RTX as the first-line treatment for patients refractory or intolerant to conventional CS, supplemented by adjuvant immunosuppression [14]. In June 2018, the FDA approved the use of RTX in the treatment of PV. In 2020, the EADV updated S2K guidelines suggested RTX alone or combined with oral prednisone as the first-line treatment for mild PV patients, and RTX combined with systemic CS for the patient of moderate to severe PV/PF [3]. Within the same year, experts from China recommended CS plus RTX as the early treatment for patients with moderate to severe PV and suggested using intravenous immunoglobulin (IVIg) during treatment with RTX.

There are two main regimens for the use of RTX in patients with pemphigus [5]. The rheumatoid arthritis regimen is two intravenous infusions of RTX 1000 mg at a 2-week interval, and the lymphoma regimen is four intravenous infusions of RTX 375 mg/m^2 at a 1-week interval [3]. For the subgroup of patients with baseline PDAI$\geq$45, Joly et al. recommended RTX maintenance therapy every 6 months. In addition, this therapy was also applicable for patients with persistent *anti*-Dsg1 antibody values of 20 IU/ml and *anti*-Dsg3 antibody values of 130 IU/ml at month 3 [3]. Moreover, the regimen of RTX plus IVIg is: during the first month, pemphigus patients receive RTX 375 mg/m^2 weekly over three weeks; in the fourth week, IVIg 2000 mg/kg is infused, followed by the same regime in the second month. In month 2, treatment of month 1 is repeated, while in months 3, 4, 5, and 6, a single infusion of RTX 375 mg/m^2 plus IVIg 2000 mg/kg is to be administered at the beginning of the month. In 6 months, each patient receives a total of 10 infusions of RTX and 6 infusions of IVIg [3].

In 2018, Tavakolpour et al. reviewed 114 studies containing 1085 different PV cases, including unresponsive childhood/juvenile or adult PV patients, women of childbearing age, and those with chronic infections with the risk of reactivation [5]. The results showed the majority of these patients well responded to RTX, some of them did not respond, and a paucity of patients experienced an exacerbation of the disease. In addition to the RTX monotherapy or its combination with conventional therapies, different novel combination therapies of RTX with immunoadsorption and/or IVIg have shown promising results. Pneumocystis carinii pneumonia and septicemia were found as the two fatal and serious adverse events associated with RTX. Similar to the adults, those with childhood and juvenile PV could be successfully treated with RTX. Administration of RTX approximately ten months before conception also was found safe and effective for a successful pregnancy [5]. In 2019, a 10-year retrospective cohort analysis in a Chinese population evaluating the long-term safety and efficacy of RTX in the treatment of pemphigus concluded that RTX has greater advantages in treating recurrent and refractory pemphigus [15]. In addition to these protocols, several studies have evaluated the effectiveness of RTX monotherapy in pemphigus [16,17]. The results showed that RTX monotherapy could be a first-line and promising option in treating mild cases of pemphigus.

However, the optimal doses and timing of maintenance therapy of RTX in the management of pemphigus are uncertain, and prognostic factors are unknown. Several relapses can occur during the chronic disease course of pemphigus [18]. Therefore, the optimal timing of maintenance dose administration to prevent relapse should be personalized based on individual patient data. Saleh

MA et al. found that the early relapsing patients tended to have higher *anti*-Dsg1 antibodies than the late relapsing patients, patients with low baseline *anti*-Dsg1 index may benefit from maintenance therapy at or after 12 months [19]. On the other hand, patients with a high initial *anti*-Dsg1 index might benefit from a maintenance RTX dose at 6 months or at least closer monitoring during the first 12 months to prevent relapse [19]. Claire M et al. identified that the initial PDAI score and the evolution of *anti*-Dsg antibody value 3 months after the initial cycle of RTX are associated with short-term relapse in patient with PV after initial treatment with RTX. And these patients with high risk for relapse may benefit from a maintenance therapy of RTX at month 6 [20]. All the above study date indicates that optimal doses of maintenance therapy with RTX are based on the prognostic factors, and additional studies are needed to examine factors associated with relapse in patients with pemphigus treated with RTX.

About the best time of starting RTX therapy, Balighi et al. suggested some differences between the efficacy and safety of starting RTX within the first 6 months after PV diagnosis or those who have received RTX at least 6 months after PV diagnosis and a history of treatment with conventional therapies [21]. They compared the clinical efficacy and safety profiles of early ($\leq$6 months) or late (>6 months) treatment of PV patients with RTX. The results showed that patients under early treatment with RTX ($\leq$6 months) may not only have a higher chance to achieve complete remission but also experience a longer time of disease remission [21]. However, further studies containing a higher number of patients and also a long follow-up period are required.

To describe rates of complete remission off therapy and relapse and identify prognostic factors for achieving complete remission off therapy after RTX therapy for pemphigus, a single-center, retrospective, cohort study was conducted by Kushner et al. [22]. The results showed that Lymphoma dosing and older age may be associated with complete remission off therapy and BMI greater than or equal to 35 may be a negative prognostic factor for complete remission off therapy after RTX therapy for pemphigus [22]. These findings help inform clinical expectations and merit evaluation in future prospective clinical trials.

However, RTX does not lead to permanent remission of the disease. Due to B-cell repopulation, almost half of the responders may experience disease recurrence within 1 year or 2 years after receiving RTX [19]. There are two main factors that may limit the effectiveness of RTX in pemphigus: (i) infusion reactions and infections; (ii) the occurrence of *anti*-rituximab antibodies (ARAs). The development of human anti-chimeric antibodies (HACA) may complicate the use of monoclonal antibodies such as RTX. In systemic lupus erythematosus, ARAs are associated with lower B-cell depletion and negative outcomes [23]. Similarly, in membranous nephropathy, ARAs neutralize RTX activity in 80% of cases and are associated with faster B-cell reconstitution and a higher relapse rate [24]. The clinical significance of ARAs in patients with pemphigus treated with RTX is currently unknown. Alexandre L et al. suggested that ARAs are frequently detected in patients with pemphigus who are treated with RTX and generally are not associated with patient outcomes. And there appears to be a high risk of relapse in only a few patients with combined ARAs, low RTX concentrations, incomplete B-cell depletion, and persistent serum *anti*-Dsg3 antibodies [25]. Even though these results need to be confirmed in larger cohorts, it is important to carefully monitor patients for any adverse drug reactions during the administration of RTX. At the same time, it is necessary to develop new generations of anti-CD20 MAb.

2.1.2. Ofatumumab, OFA

OFA is the second generation fully human type I anti-CD20 MAb [26]. Its epitope binding sites are the small and large extracellular loops of the CD20 molecule and are characterized by greater CDC and ADCC response and apoptosis induction when compared with RTX [8]. RTX depletes B cells mainly via ADCC pathways due to the linking of fragment c gamma receptors (FcγR IIIA) on natural killer cells [27]. OFA exhibits a greater potency in recruiting complement than RTX, thus exerting a higher CDC efficacy. Thus, the low FcγR IIIA pathway-dependent property of OFA may explain its better efficacy than RTX [8]. This mechanism explains why patients with adverse reactions to RTX can avoid the associated allergic reactions when using OFA. The FDA approved the use of OFA in the treatment of chronic lymphoblastic leukemia (B-CLL) in 2014. A randomized, double-blinded, placebo-controlled, phase 3 clinical trial was performed from 2013 to 2018 to investigate the efficacy, tolerability, and safety of subcutaneous injection for OFA in 37 patients diagnosed with PV (NCT01920477)ee (Table 1). Patients received subcutaneous injections of OFA 40 mg at week 0 and week 4. The use of subcutaneous OFA 20 mg was continued every 4 weeks from week 8 until week 56. The primary results of this study were that subjects initially reduced their prednisone dose to $\leq$10 mg/day and maintained the dose $\leq$10 mg/day without new or non-healing lesions for $\geq$8 weeks, with maintenance status to continue through week 60. In 2019, this trial was terminated due to a change of funding agency. In 2018, the first published case report by Rapp et al. demonstrated the successful treatment of patients with PV by OFA after developing human anti-chimeric antibodies (HACA) to RTX [28]. In 2020, Daniel et al. reported a patient with active mucocutaneous PV for 9 years and failed multiple treatments, including doxycycline, high-dose prednisone, mycophenolate mofetil (MMF), methotrexate, and RTX [29]. At last, the patient was treated with OFA using the chronic lymphocytic leukemia dosing regimen proposed by Rapp (300 mg on day one, 1000 mg on day eight, then 1000 mg every 28 days for 8 cycles). After the second infusion, the clinical symptoms of the patient improved. One month after completing nine cycles of treatment, the clinical symptoms of the patient completely disappeared [29]. These two case reports reveal that OFA has the potential to become a novel targeted therapy for PV. However, more clinical trials are necessary to demonstrate the efficiency of OFA.

2.1.3. Veltuzumab

Veltuzumab is a second-generation type I humanized anti-CD20 MAb. Its binding avidities of CD20 molecule are stronger than RTX [8]. To boost efficacy, OFA and veltuzumab have increased binding affinity to the Fc receptor on B cells and increased CDC [27]. The reason is the change of asparagine (Asn) to aspartic acid (Asp) at the 101th position in complementarity-determining region (CDR) 3 of the variable heavy chain (VH) [30]. Veltuzumab was approved by FDA as an orphan drug for immune thrombocytopenic purpura (ITP) in 2015. The main advantage of veltuzumab over RTX is that it can be injected subcutaneously and causes lower side effects than intravenous RTX [8]. In 2014, Ellebrecht et al. reported that a patient with PV who could only achieve partial remission with RTX was

successfully treated with subcutaneous injections of veltuzumab [30]. The patient was treated with two subcutaneous injections of 325 mg (188 mg/m^2) veltuzumab at a 2-week interval and was in complete remission for 2 years. However, after 2 years of treatment, the disease relapsed, and the patient received a second cycle of veltuzumab with the same dosing protocol, resulting in complete disease remission for 9 months. No serious adverse events occurred during 35 months of follow-up [30]. Unfortunately, there is no case report or clinical trial after this case, but we can speculate that subcutaneous injections of veltuzumab may become an alternative for the patient diagnosed with refractory PV.

2.2. BAFF inhibitor — VAY736 (lanalumab)

B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS), is an important immune regulatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily [31]. BAFF is important in B cell differentiation and survival [7]. In PV patients treated with RTX, the level of BAFF increases with the decrease of pathogenic antibody levels [11]. VAY736 is a fully-humanized IgG MAb targeting the BAFF receptor (BAFF-R). BAFF-R is only expressed on immature and mature B cells up to the lymphoblast stage [31]. VAY736 competitively inhibits the binding of BAFF to BAFF-R, thus blocking the signal transduction mediated by BAFF-R. In addition, VAY736 has a stronger effect on ADCC, which induces apoptosis of B cells [32]. A randomized, placebo-controlled, partial-blind, phase 2 clinical trial is currently in progress to evaluate the benefits of VAY736 in PV patients (NCT01930175) see (Table 1). In this clinical trial, 7 of 13 patients were randomized to the 3 mg/kg VAY736 group, 2 patients to the 10 mg/kg VAY736 group, and 4 patients to the placebo group. The measurement outcomes were the PDAI levels and the ABSIS scores at week 12 compared to those at baseline. The trial was completed in 2020. The PDAI score was 5.90 in the 3 mg/kg VAY736 group and 10.15 in the 10 mg/kg VAY736 group. In the placebo group, the PDAI score was 22.07 at week 12. In addition, the ABSIS scores of the 3 mg/kg VAY736, 10 mg/kg VAY736, and placebo groups at 12 weeks were 2.19, 5.55, and 16.17, respectively, lower than the baseline scores of 13.26, 16.38, and 33.75, respectively. So far, no preliminary data on this trial have been published. However, there is speculation that the BAFF inhibitor may also have a potential role in treating pemphigus disease.

2.3. BTK inhibitor — PRN1008

Bruton tyrosine kinase (BTK) belongs to the Tec family of kinases [33]. BTK is expressed by B-lymphocytes, from the pre-B to the mature B lymphocytes, including antibody-producing plasma cells [33]. It plays a crucial role in B-cell receptor activation, which is essential for the survival and function of B cells [33]. The effectiveness of BTK inhibition in pemphigus was first reported in a 51-year patient who suffered from chronic lymphocytic leukemia and developed paraneoplastic pemphigus (PNP). CLL disease control was achieved with ibrutinib and together there was a significant improvement in his pemphigus lesions. This was the first indication that ibrutinib may be added as a treatment option for pemphigus [34]. Rillzabrutinib (PRN1008) is a highly potent inhibitor of BTK with unique reversible covalent binding that has the potential to improve the safety profile compared with irreversible BTK inhibitors such as ibrutinib [35]. PRN1008 acts on a range of immune cells. It inhibits B cell activation through inhibition of the BCR. However, it doesn't cause B cell depletion or cellular cytotoxicity [36]. This is a key difference from current therapies like RTX because it doesn't provoke prolonged immune suppression [36]. Additionally, PRN1008 rapidly inhibits Ab-mediated immune cell activation through Fc-receptor signaling [33]. In a phase 1 study in 62 healthy volunteers, PRN1008 was well-tolerated following oral administration. No severe adverse events occurred during the trial. The most common adverse events were mild and mainly associated with the gastrointestinal system [36]. PRN1008 was granted Orphan Drug Designation by FDA for the treatment of patients with PV, after the encouraging results of phase II open-label cohort study examining PRN1008 in adult patients with PV (NCT02704429) see (Table 1) [37]. In this trial, 27 PV patients were enrolled, and 14 patients met the primary endpoint of CDA (no new lesions and existing lesions healed). Six patients achieved complete response by week 24, including 4 at week 12, indicating that PRN1008 alone or with a lower CS dose is safe and has rapid clinical activity in PV. Following this proof-of-concept trial, a phase 3 pivotal study (NCT03762265) of PRN1008 vs. placebo with CS taper is underway for PV. Based on these results and the vital function of BTK in B-cell development, BTK inhibitors could be a potential target for the treatment of pemphigus disease.

2.4. CAAR-T therapy

Chimeric antigen receptor (CAR) T cells targeting CD19 have proven clinical ability to induce durable remission of B cell cancers [38]. In PV, pathogenic memory B cells express *anti*-Dsg3 B cell receptors (BCRs) [39]. The researchers reasoned that by expressing Dsg3 as the extracellular domain of a chimeric immunoreceptor, cytotoxicity would become specific for only those B cells bearing *anti*-Dsg3 BCRs, providing targeted therapy for PV without general immunosuppression [40]. Such a strategy would directly eliminate surface immunoglobulin (sIg)+ *anti*-Dsg3 memory B cells and indirectly eliminate sIg−Dsg3-specific short-lived plasma cells that produce the disease-causing antibodies [41]. Thus, Ellebrecht et al. first evaluated the ability of Dsg3 CAAR-T cells to kill *anti*-Dsg3 B cells in vitro. Afterward, the efficacy of Dsg3 CAAR-T cells against AK23/AK19/AK18 target cells was tested in vivo in a PV mouse model. The results suggested that this therapy can cure the disease by generating long-term memory CAAR-T cells [42].

In 2020, Payne and her colleagues presented definitive preclinical studies enabling a first-in-human trial of desmoglein 3 chimeric autoantibody receptor T cells (Dsg3-CAART) for mucosal PV [41]. In the standard CAR T-cell approach, doctors harvest T cells from the blood of patients, modify the T cells to attack B cells, grow and expand the altered T cells in the lab, and then reinfuse these CAR T-cells into patients to seek and destroy all B cells in the body, including both lymphoma-causing and normal B cells [41]. In the Dsg3-CAART approach, the research team modified PV patients' T cells using Dsg3 as part of a decoy receptor on the surface of modified T cells,

programming them to attack and kill only the *anti*-Dsg3 antibody producing B cells [41]. Among their findings, the researchers noted a variety of effective preclinical tests of this novel approach, including: (1) Dsg3-CAART cells virtually eliminated all *anti*-Dsg3 B cells in experimental cell culture experiments using B cells from PV patients while sparing other B cells; (2) Dsg3-CAART treatment alleviated blister-like disease symptoms and decreased levels of *anti*-Dsg3 antibodies in both a passive transfer hybridoma cell line and an active immune mice model of PV, with no discernible side effects; (3) In ex vivo cultures of human cells and high-throughput membrane proteome arrays, Dsg3-CAART cells appeared to have no relevant interactions with targets other than the intended targets: B cells targeting Dsg3; (4) Dsg3-CAART manufacturing from cells collected from PV patients on immune suppressive therapy was as good as cells collected from healthy donors, except for a small subset of patients on high doses of more than one immune suppressive drug; however, cell product was achieved in all case [41].

These preclinical data guided the trial design for Dsg3-CAART and an open-label study was initiated to determine the maximum tolerated dose of Dsg3-CAART in Mucosal-dominant PV Patients (mPV) (NCT04422912)(see Table 1). Furthermore, these preclinical data give a basis that could guide the future development of CAART treatments for other antibody-mediated disorders.

3. Modulation of autoantibody (IgG) Half-Life

3.1. FcRn antagonist — efgartigimod (ARGX-113), ALXN1830(SYNT001)

The Fc receptor is a cell surface molecule of the Fc fragment of immunoglobulin (Ig), which is expressed on the surface of immune helper cells and effector cells [43]. The neonatal Fc receptor (FcRn) is important in protecting IgG from degradation and presenting antigens [43]. Efgartigimod (ARGX-113) is a human IgG1 Mab, which is an antagonist of FcRn. By blocking FcRn, the drug can reduce the circulating antibody within the blood serum [43]. Currently, an open-label, non-controlled, phase 2 clinical trial to evaluate the efficacy of ARGX-113 in patients with mild to moderate PV and PF (NCT03334058) (see Table 1)is completed [44]. In this study, 34 patients with mild-to-moderate PV or PF were enrolled and, efgartigimod was dosed at 10 or 25 mg/kg intravenously with various dosing frequencies in sequential cohorts, as monotherapy or as add-on therapy to low-dose oral prednisone [44]. The primary outcome is safety endpoints comprised. The results of the study showed that adverse events were mostly mild and were reported by 16 of 19 (84%) patients receiving efgartigimod 10 mg/kg and 13 of 15 (87%) patients receiving 25 mg/kg, with similar adverse events profiles between dose groups. A major decrease in serum total IgG and *anti*-desmoglein autoantibodies was observed and correlated with improved PDAI. Efgartigimod, as monotherapy or combined with prednisone, demonstrated early disease control in 28 of 31 (90%) patients after a median of 17 days. Optimized, prolonged treatment with efgartigimod in combination with a median dose of prednisone 0.26 mg/kg per day led to complete clinical remission in 14 of 22 (64%) patients within 2–41 weeks [44]. The clinical results of this study demonstrate that efgartigimod represents a well-tolerated potential means of achieving early disease control and complete clinical remission of pemphigus while allowing early corticosteroid tapering and efgartigimod treatment of participants with pemphigus improved their conditions and exerted an immunomodulatory effect beyond the blockade of IgG recycling [45]. Based on these data, a phase 3 randomized controlled trial is in progress to further study the efficacy and safety of efgartigimod in PV and PF (NCT04598451). Another open-label, multicenter, follow-up phase 3 trial has been conducted to evaluate the benefit of Efgartigimod PH20 SC in patients with pemphigus (NCT04598451/NCT04598477). The start date of this trial was February 2021, and the result of this trial is very promising.

ALXN1830 (SYNT001) is a humanized IgG4 MAb that binds to FcRn to disrupt the interaction of FcRn with IgG. An open-label, multicenter phase 1 B/2 trial has been completed to evaluate the safety and dosing of ALXN1830 (SYNT001) in PV or PF patients (NCT03075904). Eight patients were treated with 5 doses of ALXN1830 once a week at 10 mg/kg for 5 weeks and follow up to day 112 (termination of study). The primary outcome of the trial was the number of participants reporting treatment-emergent adverse events (TEAEs), with all eight patients experiencing at least one TEAE [46]. Headaches were the most common, with six out of eight patients experiencing headaches and 46% after the first infusion. One patient experienced two serious TEAEs, including cutaneous herpes simplex infection and methicillin-resistant *Staphylococcus aureus* infection. ALXN1830 also resulted in a rapid decrease in serum IgG levels, with a 32.5% decrease in median the total IgG nadir day 5 after the first dose, a 57.6% decrease in the median total IgG levels on day 30 compared to baseline, and a return of the median total IgG to within 25% of baseline levels at the end of the day 112 study [46]. In addition, the PDAI scores declined in five patients on day 28 and on day 84 in a sixth patient. In responders, the median PDAI activity score on day 33 was reduced to a median of 39.64% of the baseline levels. *Anti*-Dsg1 and 3 titers were reduced in 4 of the 6 patients who responded clinically. In contrast, two patients with worsening clinical symptoms had elevated levels of *anti*-Dsg1 and no significant change in *anti*-Dsg3 levels [46]. This proof-of-concept study of ALXN1830 in the treatment of pemphigus showed clinically meaningful efficacy and an overall acceptable safety and tolerability profile. Based on the results of this pilot study, it is important to develop FcRn-targeted therapies and the potential application of ALXN1830 therapy in the treatment of pemphigus and associated blistering diseases have been supported.

4. Inhibition of inflammatory markers

4.1. IL-4Rα antibody — dupilumab

Interleukin-4 (IL-4) is a cytokine produced by Th2 cells, which has been reported to play a key role in PV [47]. Dupilumab is a recombinant fully human IgG4 Mab targeting the IL-4RA protein [48]. The binding of dupilumab to IL-4RA inhibits the signaling of IL-4 and IL-13 and blocks the downstream signaling of the JAK/STAT pathway involved in the inflammatory process [49]. IL-4 has

been approved by the FDA for the treatment of moderate to severe atopic dermatitis, and it has also been used to treat asthma and chronic rhinosinusitis with nasal polyposis. In addition, recent studies have shown that IL-4 is effective in bullous pemphigoid [50]. Several studies reported that IL-4 is elevated in patients with PV and PF [51]. Chen et al. described a 35-year-old male with refractory pemphigus vulgaris and pulmonary tuberculosis who failed to respond to traditional therapies but reached stable improvement when treated with dupilumab combined with methylprednisolone, *anti*-TB regular regimen, and antibiotics plus low-dose IVIG [51]. Considering the ability of dupilumab to inhibit the IL-4 receptor and the critical role of IL-4 in patients with pemphigus as recently discussed by the authors, we believe that dupilumab may be an effective treatment for patients with pemphigus [49]. Although there are no clinical trials on the role of dupilumab, it is theoretically a promising treatment for pemphigus. Therefore, further research and clinical trials related to the use of dupilumab in the treatment of pemphigus are recommended to assess the efficiency of this emerging drug [47].

4.2. IL-17 blockade

Interleukin-17 (IL-17) is an important pro-inflammatory cytokine that includes 6 members from IL-17 A to IL-17 F [52]. IL-17 A is mainly produced by the $CD4^+$ helper T cells (Th17 cells), which is related to the pathogenesis of many immune-mediated diseases, such as pemphigus and psoriasis. Yuan et al. reported that in patients with pemphigus, Dsg3-reactive B cells were found in lesional skin and produced pathogenic Dsg3-specific antibodies in vitro [39]. B cells in the dermis can also secrete pathogenic auto-antibodies with T cells that produce IL-17 and IL-21. In this study, serum levels of IL-17 in PV patients showed significant differences compared to healthy controls. Polakova et al. found a significant induction of IL-17 and IL-21 in CD154 + $CD4^+$ T cells from PV patients compared to HC, meanwhile, CD154- $CD4^+$ T cells remained mainly unaffected regarding their cytokine expression after antigenic stimulation [40]. These findings strongly suggest that CD154 as a specific activation marker in PV, expressed by antigen-specific $CD4^+$ T cells, is critical during the pathogenesis of PV [40]. These results showed that peripheral blood T cell subsets of patients with active pemphigus are dominated by IL-17-producing Th and Tfh cell subsets. Moreover, upregulation of IL-17 was seen to associate with antigen-specific activation, therefore lending themselves as potential therapeutic targets in pemphigus [40]. Zou et al. found an over representation of $CD4^+$ tissue-resident memory T (T_{RM}) cells which accumulated significantly in pemphigus skin lesions. These $CD4^+$ T_{RM} cells expressed a specific set of T follicular helper cell–related costimulatory molecules and remained in the lesions produced IL-17 A and IL-21 [39]. Hence, future therapies targeting the maintenance of pathogenic $CD4^+$ T_{RM} cells in pemphigus lesions or even other relapsing diseases represent an attractive approach [39]. Now, some IL-17 blockades, such as secukinumab, brodalumab, and ixekizumab have been approved by the FDA for the treatment of psoriasis [53]. Kohlmann et al. described a patient with initially assumed coexisting PF and psoriasis pustulosa (PP) who was treated with the *anti*-IL-17 antibody secukinumab [54]. The clinical skin picture markedly improved and the level of *anti*-desmoglein-1 antibodies decreased; however, with the prolongation of injection intervals of secukinumab, autoantibody levels started to rise again. A dose-dependent effect of secukinumab on autoantibody production in PF is suspected [54]. However, there are some cases reported that patients with psoriasis developed PF during brodalumab treatment [55, [55]. It may be possible that the concentration of IL-17 was temporarily increased in the dermis at the beginning of brodalumab administration, causing PF. Another possibility is that brodalumab exposed the Dsg1 antigen by binding to the IL-17 receptor in keratinocytes. Further studies will disclose a possible association between IL-17 blockades and PF development [56]. However, according to the important role of IL-17 in pemphigus, although there are no clinical trials on the role of IL-17 inhibitors, it is theoretically a promising treatment for pemphigus. Therefore, further research and clinical trials related to the use of IL-17 inhibitors in the treatment of pemphigus are recommended.

4.3. TNF-α inhibitor

Studies have shown that tumor necrosis factor (TNF-α) is widely expressed in skin lesions of PV patients. The serum concentrations of TNF-α correlate with disease activity and IgG auto-antibody titers [57]. Assaf et al. found the role of TNF-α in mediating the deleterious effect of increased ST18 expression in PV skin [57]. Taken collectively, these observations provide additional in vivo evidence for the TNF-α role in the pathogenesis of PV. Treatment with various TNF-α-blocking agents has yielded variable results in refractory pemphigus patients [57]. Etanercept (ETN) is a recombinant fusion protein that can be used as a competitive inhibitor of TNF-α, which has been approved for the treatment of psoriasis [58]. In 2020, Didona et al. reported a patient affected by erythromycin-induced PF and mild plaque psoriasis [58]. As the patient refused to receive systemic CS, etanercept 50 mg subcutaneous injections at 1-week intervals were administered. After the second injection, the clinical symptoms of the patient improved significantly [58].

4.4. mTOR pathway inhibitor - rapamycin

The mammalian target of rapamycin (mTOR) is an atypical protein kinase that controls growth and metabolism in response to nutrients, growth factors, and cellular energy levels [59]. Aberrant mTOR pathway activity is involved in many autoimmune diseases. Lai et al. investigated the correlation between mTOR pathway (PI3K/AKT/mTOR/p70S6K) activity and the imbalance in T helper 2/regulatory T (Th2/Treg) cells in peripheral blood of PV patients [60]. The results showed that rapamycin inhibited Th2 cell differentiation and promoted Treg cell differentiation in vitro, indicating a close relationship between mTOR pathway activity and the imbalance in Th2/Treg cells [60]. This study points towards a new therapeutic strategy for PV that involves blocking or interfering with the signaling pathway and associated enzymatic mechanisms that induce blistering. Regrettably, a clinical trial for the evaluation

of sirolimus (rapamycin) for the treatment of pemphigus has no results as the study has been terminated early by the investigator (NCT01313923) see (Table 1). Besides, the activation of the mTOR pathway (PI3K/AKT/mTOR/p70S6K) is important in the pathogenesis of PV and the balance of Th2/Treg cells, which may be a novel treatment target for PV [61].

5. Immunological checkpoint receptors and agonists

Immune checkpoint receptors, such as Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), play critical roles in maintaining immune tolerance to self-antigens and controlling autoimmunity [62]. CTLA-4 promotes regulatory immune responses and suppresses the aberrant immune response and affects both $CD4^+$ and $CD8^+$ T cells toward exhausting T cells through direct inhibition. The critical role of CTLA-4 in the induction of regulatory responses had led to emerging of abatacept (CTLA-4Ig) for the treatment of rheumatoid arthritis [63]. A study by Abida et al. found that the susceptibility to PF was located in the proximal and the distal 3′ flanking region of the CTLA4/ICOS promoter in the Tunisian population in 2020 [64]. Therefore, by analyzing the associations between common polymorphisms in the 2q33 cluster and susceptibility to PV or PF in different populations, this study may provide new perspectives for an effective yet personalized treatment for pemphigus patients [64]. Recently, a crossover, randomized, and multi-center study to evaluate the efficacy and safety of abatacept vs. mycophenolate mofetil (MMF) in the treatment of PV is recruiting (NCT05303272). This study evaluates the efficacy, tolerability, and safety of abatacept injection for abatacept SC 150 mg administered once a week in subjects with PV. Ernst et al. reported an increased expression of the checkpoint receptors PD-1 in lesional skin and the serum levels of soluble PD-1 of patients with PV [65]. That suggested there is a defect in the PD-1 pathway of PV patients. Moreover, many recent studies have highlighted the advantages of immune checkpoint modulators in treating autoimmune diseases. Thus, targeting CTLA4 and PD-1 pathways could be a potential aim for future therapies for PV. However, there are many issues needed to be addressed in future research.

6. Inhibition of the blister-inducing activity of autoantibodies

Topical modulation of blistering induced by PV autoantibody is a key part of the treatment of PV patients. Berkowitz P et al. found that p38 MAPK inhibitors can prevent skin blistering in PV mice by inhibiting PV IgG-activated signaling in epidermal cells targeted by PV autoantibodies [66]. Egu et al. demonstrated that blistering could be prevented by inhibiting p38 MAPK in the human epidermis [67]. In addition, they found that p38 MAPK inhibition was not effective in preventing autoantibody-induced mucosal blistering in pemphigus injected with mucosal-dominant PV [68]. So far, only a few clinical trials have shown the effect of p38 MAPK inhibitors in asthma, Alzheimer's disease, cancer, and rheumatoid arthritis. Burmester et al. performed an unbiased screening in a complex biological system using 141 low MW inhibitors from a chemical library to find novel therapeutic targets for blocking acantholysis [9]. The result showed that MEK1, TrkA, PI3Kα, and VEGFR2 were involved in PV IgG-induced skin pathology and could be new treatment targets for PV [9]. According to the role of these targets on the pathogenesis of PV, the use of these inhibitors in PV may be a particularly attractive and practical approach for treating life-threatening autoimmune skin diseases.

7. Future perspectives

As a new treatment method, targeted therapy is gaining increasing popularity as it is proven to be increasingly efficacious in treating autoimmune bullous disease (AIBD). The most notable targeted therapy is RTX, while the most novel therapy is the immune checkpoint receptors. Due to the inherent nature of pemphigus disease, targeted therapy is undeniably the direction of the future research area in providing a more favorable disease outcome for patients, especially those who do not respond to conventional treatments. With leaps in immunological therapy and ongoing trials on different types of targeted therapies, we are confident that pemphigus disease will be treated more effectively. A better understanding of the interaction between immune cells, autoantigens, autoantibodies, and signal molecules in pathogenesis disease will promote new insights in developing more strategic treatment modalities.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

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