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Translational autoimmunity in pemphigus and the role of novel Bruton tyrosine kinase inhibitors

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ABSTRACT

Bruton tyrosine kinase (BTK) is involved in a multifarious inflammatory and autoimmune process. As a result, BTK has emerged as a promising novel remedial target for amalgamated autoimmune diseases. Medicament corporations have recently devoted considerable attention to the evolution of BTK inhibitors. Pemphigus is an uncommon and often fatal autoimmune illness. Blisters and erosions on cutaneous surfaces and mucous membranes are crippling symptoms of pemphigus vulgaris, which are caused by immunoglobulin G autoantibodies binding to keratinocyte proteins, resulting in keratinocyte adhesion defects. Although systemic corticosteroids and adjuvant medications are used to treat pemphigus, some patients are resistant to these. BTK inhibitors inhibit B-cell signaling, which is clinically useful in treating pemphigus. Assorted clinical trials are underway to assess the safety, tolerability, and pharmacokinetics of distinct BTK inhibitors, including PRN473 and remibrutinib. The current review evaluates translational autoimmunity in pemphigus and discusses BTK inhibitors in the treatment of pemphigus.

1. Introduction

Immunoglobulin G (IgG) autoantibodies, in contrast to epidermal adhesion proteins, cause pemphigus, a severe autoimmune disease. These autoantibodies append to the epidermal adhesion protein desmoglein (Dsg), culminating in intraepidermal blistering, acantholysis, and erosion in the relevant fields [1,2]. Pemphigus can be classified into various subtypes. Pemphigus vulgaris (PV), which causes agonizing oral erosions, and pemphigus foliaceus (PF), which causes skin lesions, are the two primary categories. A few types of this disease can be lethal if left untreated [3].

During the induction stage of pemphigus, high-dose of oral corticosteroids (CS) are indicated as first-line treatment, with decreasing doses throughout the maintenance period, according to Japanese recommendations [4]. Treatment of pemphigus involves the administration of a low-dose oral steroid to maintain remission. Prednisolone is the preeminent preference for introductory therapy during the consolidation phase. If the treatment outcomes are deduced to be clinically irresolute, other approaches such as steroid pulse therapy, immunosuppressants, intravenous immunoglobulin treatment at a high dose, and plasma exchange should be considered. Despite the use of these standard treatments, achieving remission remains a challenge. Furthermore, many individuals who respond to these traditional treatments have various adverse effects [5]. Refractory instances of treatment with rituximab have been recently reported. However, not all patients benefit from rituximab because of the risk of dangerous adverse effects and long-term B-cell depletion [6]. Furthermore, multi-hour rituximab infusion depletes abundant healthcare assets and is awkward for patients [7,8]. As a result, state-of-the-art therapeutic approaches with contrastive modus operandi are required [9]. Bruton tyrosine kinase (BTK), a crucial modulator of B-cell receptor (BCR) signaling, curtails costimulatory molecule expression, BCR-aroused propagation, and antibody manufacturing in B-cells [10–12]. Therapeutics for B-cell reduction have determined that BTK is a primary factor in the pathogenesis of pemphigus [13]. This review aimed to evaluate translational autoimmunity in pemphigus and the effectiveness of BTK inhibitors in the management of pemphigus.

2. Methodology

Using the appropriate key terms, a literature search was conducted in the following databases: PubMed, MEDLINE, Scopus, Google Scholar, and Cochrane. The author primarily searched for articles about autoimmunity in pemphigus and aspects of BTK inhibitors in its management. Fig. 1 shows the results of the initial literature search, which yielded 562 publications. All published articles were reports describing

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the role of BTK inhibitors in the treatment of pemphigus; articles published in the English language were included in this review (Fig. 1).

3. Public health and pemphigus

PV is the most common subtype of pemphigus, with a predisposition towards Ashkenazi Jews [14–16]. This has been linked to the ubiquity of stipulated HLA class II genes in Jewish individuals [17].

In the Caucasian population, the incidence of sporadic PF is 0.04 per 100.000 people yearly. Only approximately 20% of pemphigus cases are of sporadic PF type [15,17]. Many HLA alleles are affiliated with higher risks of PF [18,19].

4. Bruton tyrosine kinase enzyme

BTK is an important regulator of immunity because of its role in the maintenance of B-cells and immune cells related to innate immunity. It is an essential component of BCR, Fc receptors, and other innate immunity related pathways [20,21]. Additionally, BTK is necessary for Ab (IgG and IgE)-mediated immune complex signaling through the concorded FcgR and FceR signaling pathways [20,21]. The importance of innate immune cells in immunologically mediated dermatological diseases is unappreciated [9,22]. In such cases, neutrophils, eosinophils, and mast cells are activated and accumulate in the lesioned skin, which is ordinarily identical to tissue impairment and disease acerbity, and myriad BTK-reliant cells lead to cutaneous inflammation [9,22]. These resident and trespassing immune cells can be treated topically or systemically.

BTK inhibition has been proven in preclinical research to determine the specificity of immune-mediated cutaneous disorders. BTK inhibitors have been demonstrated to curtail proteinuria, the kidney microenvironment, and cutaneous brims in heterogeneous rodent models of arthritis and lupus [7,8]. In representations of the Ab-induced Arthus reaction and murine passive cutaneous anaphylaxis, BTK inhibitors also prevent acute skin inflammation and vasculitis [23]. BTK inhibition has been detailed in clinical trials as an effective treatment for various B-cell cancers [10]. Ibrutinib, acalabrutinib, and zanubrutinib are the only three covalent BTK inhibitors approved by the FDA for use in patients with B-cell malignancies and autoimmune disorders [11]. Diverse orally administered BTK inhibitors, including fenebrutinib, rilzabrutinib (PRN1008), remibrutinib, tolebrutinib (PRN2246/SAR442168), and evobrutinib, are available for treatment of various immune-mediated diseases, including multiple sclerosis and pemphigus [7,24].

PRN473 is a BTK covalent impediment molecule that has been

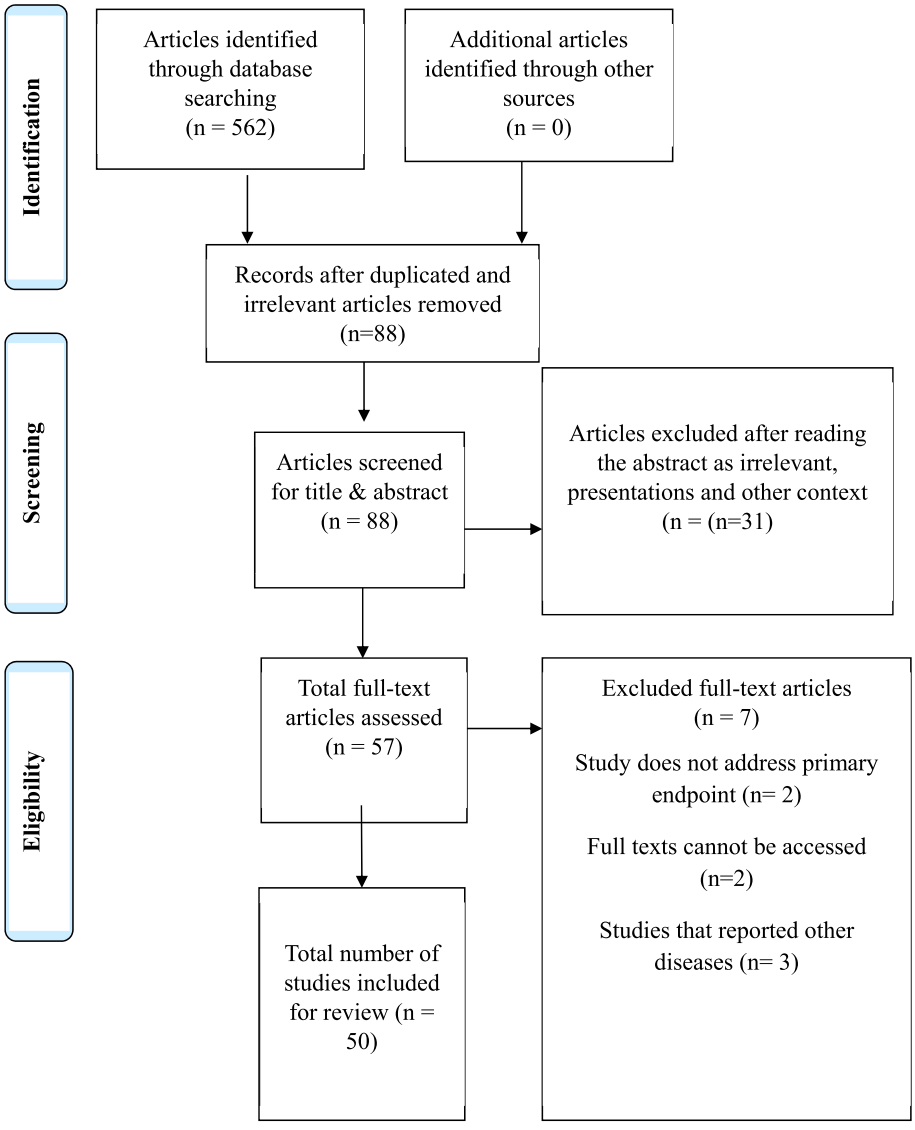

Fig. 1. PRISMA flow chart.

applied topically and has been created with tailored covalency to show durable and transitional BTK binding [24,25]. PRN473 binds to BTK with both noncovalent and covalent interactions, resulting in increased efficacy and perpetuation, but reduced coupling to off-target kinases [24]. Because PRN473 hinders the development and progression of immune-mediated skin diseases, topical administration is important in cutaneous disorders. This results in a local therapeutic effect, with the least amount of systemic unfolding. PRN473 curbs mast cell and basophil activation induced by IgE (FceR), monocyte activation induced by IgG (FcgR), and neutrophil migration mediated by IgG (FcgR) [26]. When administered to treat canine PF, oral PRN473 showed potential and a decent tolerance profile [27].

5. Translational autoimmunity in pemphigus

In pemphigus, CD4 autoreactive T cells targeting Dsg proteins initiates an autoimmune cascade in genetically susceptible individuals, and evokes B lymphocytes to synthesize anti-Dsg antibodies [28].

In PV and PF, precise point antigen autoantibodies promote keratinocyte detachment (acantholysis) and blister development (PF). Dsg3 was observed to be located deep in the epidermis, whereas Dsg1 was observed in the superior stratum of the epidermis. However, when both forms of Dsgs exist, only one form is inhibited, while contrasting objects will recoup. When a monomeric configuration of Dsg exists, autoantibody activity in the lesions ceases. In distinct pemphigus forms, this rationale explains the observation of target antigen-specific autoantibodies found in the skin and mucosa inequitably [29]. These phenomena are illustrated in Fig. 2.

A definite mechanism of acantholysis development in pemphigus is still being investigated. Three factors resulting from the binding of anti-Dsg IgG are reported: desmosomal activity is lost, blisters form as a result of Dsg *trans*-interaction due to steric obstruction, and amended outside-in signaling by pemphigus autoantibodies [28,29].

Pemphigus is also recognized as a desmosome-redesigning disease because superstratum Dsg maintenance undergoes remodeling, resulting in the lack of this surface protein. A decrease of Dsg initiates development of acantholysis. Desmosomes are further susceptible to postliminary depletion processes as their adherence activity decreases [30].

Pemphigus IgG-induced acantholysis occurs due to the stimulation of keratinocyte intracellular signaling pathways; cytoskeletal architectures are disrupted by this signaling phenomenon. These contrasting characteristics are not similar to other adhesion proteins. Ca^{2+} influx occurs when Dsg1 is targeted [31–34].

PV IgG tethers to Dsg3 and activates desmosomal signaling pathways, stimulating heat shock protein (HSP27) and p38 mitogen-activated protein kinase (MAPK), in addition to cytoskeletal disengagement. These observations come from studies that adopted PV Dsg-3 autoantibodies to activate desmosome signaling in human keratinocyte cells. Both p38MAPK and HSP27 are involved in the maintenance of cytoskeletal components, such as actin and intermediate filaments. These findings imply that signaling is effective in PV IgG-induced acantholysis. Eventually, restraining desmosome signaling by HSP27 and p38MAPK phosphorylation has been considered as a prospective therapeutic strategy for PV [35].

The above-mentioned PV IgG mediated internalization of surface proteins takes only a few hours. In mouse models of pemphigus, p38MAPK regulates surface Dsg3 internalization and degradation [36]. Downregulation of Dsg enhances intracellular adhesion and mitigates the acantholytic effects of pathogenic IgG [37].

In the epidermis of pemphigus patients, activation of intracellular signaling pathways mediated by HSP27 and p38MAPK was also observed, which was evident from the increased phosphorylation of these two proteins [38]. Dermal infiltrates in pemphigus lesions encompass interstitial and perivascular neutrophils and eosinophils, which are mobilized by the innate immune system. Correspondingly, therapeutic targets are found not only in adaptive but also in innate immune pathways. The advantage of using BTK inhibition to treat pemphigus is that a selective BTK inhibitor can target heterogeneous autoimmunity pathways, such as inhibition of monocyte and macrophage cytokine release caused by FcR, BCR-mediated B-cell pathways modulation, neutrophil passage, mediator absolution, and FcR-induced mast cell degranulation.

6. Role of BTK in the treatment of pemphigus

In clinical trials, BTK inhibition has been an effective remedy for an

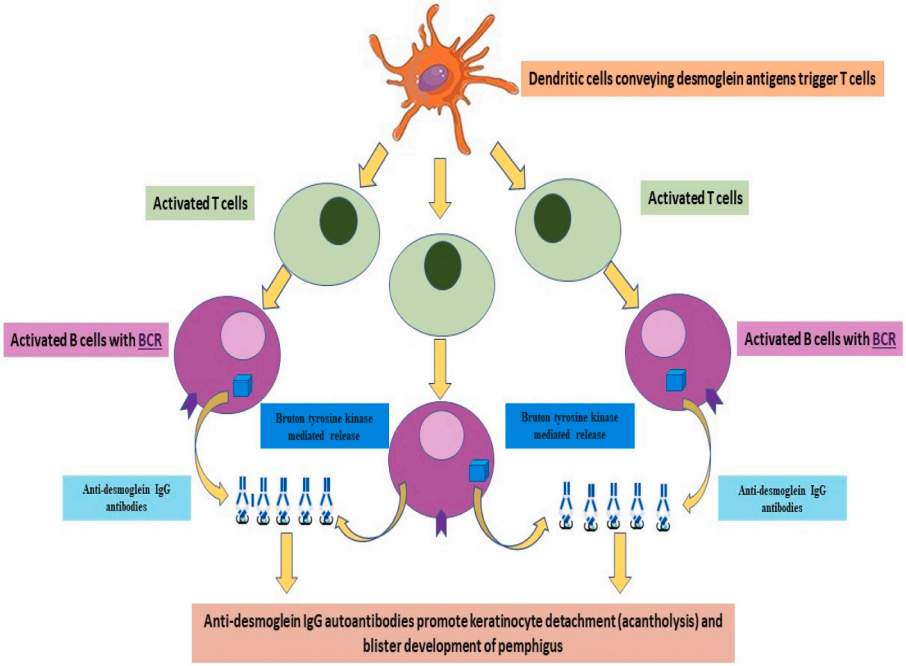

Fig. 2. Interplay of activated T cells and activated B cells setting of BTK-mediated anti-DSG antibodies which ultimately culminates in acantholysis of pemphigus.

array of B-cell malignancies. PRN473 is a BTK covalent blocker that has been utilized topically and has been created with customized covalency to show stable, reversible BTK binding [36,37]. PRN473 binds to BTK with both noncovalent and covalent contacts, resulting in high potency and sustained inhibition but sparse binding to off-target kinases [36]. As PRN473 inhibits the initiation and progression of immune-mediated cutaneous diseases, topical administration is especially significant. This produces localized therapeutic effects with the least systemic vulnerability. PRN473 inhibits mast cell and basophil activation mediated by IgE (FceR), monocyte activation mediated by IgG (FcgR), and neutrophil migration mediated by IgG (FcgR) [38]. Oral PRN473 showed effectiveness and a good tolerance profile in a canine model [39]. A phase 2 trial evaluating the effectiveness, tolerance profile, and pharmacokinetics of PRN473 in patients with mild to moderate atopic dermatitis is ongoing.

6.1. Ibrutinib

BTK inhibition was first used to treat pemphigus in an elderly patient with chronic lymphocytic leukemia (CLL) and acquired paraneoplastic pemphigus (PNP). Ibrutinib was administered to manage his CLL condition, and his pemphigus lesions ameliorated substantially as a result. This showed that ibrutinib could for treatment of pemphigus therapeutics [39]. A case study by Ito et al. [40] reported that a composite of ibrutinib and rituximab significantly treated PNP in a 62-year-old man. Furthermore, a few case reports have shown the efficacy of rituximab in patients with PNP associated with B-cell lymphomas [41,42].

6.2. Rilzabrutinib

Rilzabrutinib (PRN1008) is a robust BTK inhibitor with unique reversible covalent binding that potentially bolsteres the safety of this molecule in contrast to irreversible BTK inhibitors such as ibrutinib. In a phase 1 study, oral rilzabrutinib was well-tolerated by 62 healthy volunteers. During the trial, no serious adverse effects occurred. However, mild side-effects are frequent and mostly related to the gastrointestinal system [43]. A distinct BTK inhibitor, PRN473, exhibited promise in animal studies, but was less effective compared to rilzabrutinib in humans [27]. The FDA has granted rilzabrutinib orphan drug status for the cure of PV cases [44]. In a canine model PF study, during the first two weeks of treatment with rilzabrutinib, all dogs demonstrated reduction in lesions and canine PDAI score, and by 20 weeks, all dogs had attained near-complete remission [45]. Rilzabrutinib, singularly or amalgamated with low doses of CS, was found to be safe in patients with PV and had an efficient and fast clinical response [46]. Currently, phase 3 trials (PEGASUS; NCT03762265) on the efficacy of rilzabrutinib with CS in the treatment of PV are ongoing.

6.3. Tirabrutinib

Tirabrutinib hydrochloride (ONO/GS-4059), also known as tirabrutinib, is a broad-range oral BTK inhibitor, which has recently been licensed in Japan for the treatment of plasma cell lymphoma, primary lymphoma of the central nervous system, and Waldenstrom macroglobulinemia [3]. Tirabrutinib inhibits increase in culprit protein levels in lupus-prone animal and human B-cells and reduces stimulation-induced IgG production (unpublished findings) [47]. This molecule is designed to inhibit the IgG autoantibody-mediated signaling pathway involved in the pathogenesis of pemphigus pathogenesis and provide an alternative therapy for resistant pemphigus. Yamagamia et al. [3] conducted a phase II trial to evaluate the safety and efficacy of tirabrutinib in patients with refractory pemphigus. Sixteen patients were included in this study. After 6 months of treatment, the primary endpoint was reached in 18.8% of all patients (3/16; 95% confidence interval, 6.6%–43.0%). Eight patients (50%) achieved complete remission by week 52, while 10 patients (62.5%) achieved remission.

6.4. Remibrutinib

Remibrutinib (LOU064) is an orally administered, covalent BTK inhibitor. Remibrutinib is a novel type of enzyme blockers with high specificity and potency. As a result, remibrutinib has fewer side-effects than its ancestor molecules [48]. CD203c inhibition was used to assess basophil suppression by remibrutinib, with positive outcomes observed with a 2/day dose [49]. Kaul et al. [50]. reported that remibrutinib exhibited promising blood and cutaneous pharmacodynamics with an encouraging safety profile, providing alternative therapeutic options for diseases driven by B cells, basophils, and mast cells, such as Sjögren syndrome, allergic asthma, and chronic spontaneous urticaria. A phase 1 trial assessing the safety and tolerability of remibrutinib in healthy volunteers and volunteers with atopic diathesis and atopic dermatitis is ongoing. A phase 2 trial of remibrutinib was conducted to examine the efficacy and safety of the drug in adults with chronic spontaneous urticaria (CSU) who were not managed with H1-antihistamines. In addition, a phase 3 trial of remibrutinib to investigate the efficacy, safety, and tolerability for 52 weeks in adult patients with CSU inadequately controlled by H1-antihistamines will be initiated.

A summary of contemporary evidence on BTK inhibitors for pemphigus is presented in Table 1.

7. Conclusion

Pemphigus refers to a range of autoimmune blistering disorders that damage the mucous membranes and skin. The disease shows frequent recurrence and presents a major threat to patients' quality of life. BTK plays an important role in the immune system. Targeting translational autoimmunity in pemphigus using BTK inhibitors is an exciting research topic. Compared to rituximab, other BTK inhibitors offer a novel archetype for the treatment of autoimmune disorders. The persistent clinical morbidity burden and potential fatality in patients with pemphigus have encouraged clinical dermatologist to look beyond routine care. This pursuit of better management of patients with protracted pemphigus can end with BTK inhibitors. However, more RCTs are required to further analyze the safety and efficacy of BTK inhibitors.

Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

Data availability

Data sharing does not apply to this article as no datasets were

Table 1
Bruton tyrosine kinase inhibitors in pemphigus [3,40,43,46].

Medicine name	Study phase	Clinical trial identifier and end point
Rilzabrutinib PRN1008	Phase I	ACTRN12614000359639 Orally administered rilzabrutinib was well-tolerated, safe, and attained high levels of Bruton tyrosine kinase in peripheral mononuclear cells
	Phase II	NCT02704429 (completed) Rilzabrutinib alone, or with lower corticosteroid doses, was safe, with rapid activity in pemphigus vulgaris.
	Phase III	NCT03762265 (active, not recruiting)
Tirabrutinib GS-4059	Phase II	JapicCTI-184231 Tirabrutinib was safe, augmented remission and lessened required corticosteroid dose in cases of refractory pemphigus.
Ibrutinib	Case-study	Ibrutinib combined with rituximab fully treated the paraneoplastic pemphigus

generated or analysed during the current study.

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Declaration of competing interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Dr. Piyu Parth Naik.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2022.100156.

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