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REVIEW ARTICLE

Bruton's tyrosine kinase inhibition—An emerging therapeutic strategy in immune-mediated dermatological conditions

Pedro Mendes-Bastos[1] | Ana Brasileiro[2,3] | Pavel Kolkhir[4,5,6] | Stefan Frischbutter[4,6] | Jörg Scheffel[4,6] | Sherezade Moñino-Romero[4,6] | Marcus Maurer[4,6]

[1]Dermatology Center, Hospital CUF Descobertas, Lisbon, Portugal

[2]Department of Dermatology, Hospital Santo António dos Capuchos, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

[3]NOVA Medical School, Universidade NOVA de Lisboa, Lisbon, Portugal

[4]Dermatological Allergology, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[5]Division of Immune-Mediated Skin Diseases, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

[6]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

Correspondence
Pedro Mendes-Bastos, Dermatology Center, Hospital CUF Descobertas, Rua Mário Botas, 1998-018 Lisboa, Portugal.
Email: pmendesbastos@gmail.com

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Abstract

Bruton's tyrosine kinase (BTK), a member of the Tec kinase family, is critically involved in a range of immunological pathways. The clinical application of BTK inhibitors for B-cell malignancies has proven successful, and there is strong rationale for the potential benefits of BTK inhibitors in some autoimmune and allergic conditions, including immune-mediated dermatological diseases. However, the established risk-to-benefit profile of "first-generation" BTK inhibitors cannot be extrapolated to these emerging, non-oncological, indications. "Next-generation" BTK inhibitors such as remibrutinib and fenebrutinib entered clinical development for chronic spontaneous urticaria (CSU); rilzabrutinib and tirabrutinib are being studied as potential treatments for pemphigus. Promising data from early-phase clinical trials in CSU suggest potential for these agents to achieve strong pathway inhibition, which may translate into measurable clinical benefits, as well as other effects such as the disruption of autoantibody production. BTK inhibitors may help to overcome some of the shortcomings of monoclonal antibody treatments for immune-mediated dermatological conditions such as CSU, pemphigus, and systemic lupus erythematosus. In addition, the use of BTK inhibitors may improve understanding of the pathophysiological roles of mast cells, basophils, and B cells in such conditions.

KEYWORDS
Bruton's tyrosine kinase inhibitor, chronic spontaneous urticaria, fenebrutinib, pemphigus, remibrutinib

Abbreviations: AE, adverse event; BCR, B-cell receptor; BLNK, B-cell linker protein; BLyS, B-lymphocyte stimulator; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CSU, chronic spontaneous urticaria; CU-BAT, chronic urticaria–basophil activation Test; DSG, desmoglein; GM-CSF, granulocyte-macrophage colony-stimulating factor; HS, hidradenitis suppurativa; IgE, immunoglobulin E; IgG, immunoglobulin G; IP3, inositol-3,4,5-phosphate; LYN, Lck/Yes novel tyrosine kinase; MC, mast cell; NK, natural killer; PLCγ2, phospholipase C gamma 2; SLE, systemic lupus erythematosus; SLP-76, SH2-domain-containing leukocyte protein of 76 kDa; SYK, spleen tyrosine kinase; TLR, toll-like receptors.

1 | INTRODUCTION

Almost 70 years ago, Ogden C. Bruton described the first case of agammaglobulinemia in an 8-year-old boy suffering from severe recurrent sepsis.[1] The underlying cause of this immunodeficiency remained unclear until the discovery, in the early 1990s, of a cytoplasmic protein tyrosine kinase involved in B-cell development.[2,3] The X-chromosome-restricted mutations in this kinase, later named Bruton's tyrosine kinase (BTK), were established to be directly associated with X-linked agammaglobulinemia.[4,5]

Owing to its crucial role in B-cell development, migration, and activation, BTK became—and remains—the subject of intensive study. It has been demonstrated that BTK plays a key role in the signaling cascade of receptors such as the B-cell receptor (BCR), Fc receptors, chemokine receptors, toll-like receptors (TLR), and CD40.[6–12] Further studies revealed the expression of BTK also in non-B cells such as mast cells (MCs), natural killer (NK) cells, T cells, macrophages, neutrophils, monocytes, and basophils.[11,13–17]

Based on these observations, the potential of BTK as a therapeutic target became apparent, and a series of inhibitors were developed. Ibrutinib (PCI-32765) became the first BTK inhibitor available for clinical use, approved in 2014 for the treatment of B-cell malignancies.[18,19] Subsequently, BTK has emerged as a promising therapeutic target for a number of malignant and non-malignant disorders,[20–22] including various immunoglobulin E (IgE)-mediated diseases driven by MCs and basophils.[16]

Here, we review the current understanding of the role of the BTK pathway and consider the potential value of pharmacological inhibition of BTK as a therapeutic strategy in immune-mediated dermatological conditions such as chronic spontaneous urticaria (CSU), pemphigus, and systemic lupus erythematosus.

2 | ROLE AND RELEVANCE OF BTK IN HEALTH AND DISEASE

2.1 | Role in signaling cascades in B cells and MCs

BTK is a member of the Tec family of tyrosine kinases.[23] It forms part of signaling cascades triggered by surface receptors such as the BCR in B cells and the high-affinity IgE receptor FcεRI in MCs.[24,25] Activation of BTK correlates with increased phosphorylation of two regulatory tyrosine residues.[26] BTK is phosphorylated at Y551 (site 1) by kinases activated upstream of BTK, such as spleen tyrosine kinase (SYK) or members of the SRC family kinase (e.g., LCK/YES novel tyrosine kinase; LYN).[12,27] BTK then autophosphorylates at Y223 (site 2) in the SH3 domain,[28] enabling association with adapter proteins such as SH2-domain-containing leukocyte protein of 76 kDa (SLP-76)[29] or B-cell linker proteins (BLNKs).[30] This leads to phosphorylation of phospholipase C gamma 2 (PLCγ2).[31] Activated PLCγ2 generates inositol-3,4,5-phosphate (IP3) and also activates protein kinase C via diacylglycerol, resulting in calcium release and activation of transcription factors such as NF-κB and NFAT.[12] Aside from integrating BCR- or FcεRI-derived signals, BTK is also involved in other pathways such as chemokine-mediated homing of pre-B cells into lymphoid organs or TLR-mediated signaling, as well as inhibition of FcγR signaling and inflammation driven by IgG immune complexes.[12,32,33] The role of BTK in signaling cascades in various cell types and its influence over multiple physiological processes is summarized in Figure 1.

2.2 | Role in B-cell malignancies and other pathologies

Bruton's tyrosine kinase activity is crucial to maintain B-cell survival, proliferation, and differentiation. It acts as a central node in the BCR signaling that drives B-cell malignancies such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), follicular lymphoma, multiple myeloma, and marginal zone lymphoma.[12] The involvement of BTK in a range of other immunological pathways implicates it in the pathophysiology of inflammatory and systemic autoimmune disorders, as well as in allergic responses.

2.2.1 | BTK signaling in autoimmune responses

B-cell-mediated systemic autoimmune diseases are associated with activation of autoreactive B cells and their differentiation into autoantibody-producing cells.[22] Consistent with this, treatment with rituximab, an anti-CD20 monoclonal antibody, which results in the depletion of mature B cells, has demonstrated clinical benefits in certain autoimmune conditions.[34] Studies have since revealed increased BTK expression in B cells of patients with systemic autoimmune diseases; indeed, there is some evidence for a correlation of BTK protein levels with autoantibody production.[22,35] It appears that BTK can modulate signaling, such that overexpression leads to autoimmunity while decreased levels improve autoimmune disease outcomes.[32]

2.2.2 | BTK signaling in allergic responses

The binding of an allergen to its specific IgE triggers crosslinking and activation of high-affinity FcεRI on the surface of MCs and basophils.[36] The subsequent signaling cascade involves the phosphorylation of SYK and then BTK, and results in the release of mediators including cytokines.[16,36] Consistent with this, *in vitro* analyses have demonstrated that BTK inhibition is associated with reduced mediator release in human basophils[37] and reduced IgE-mediated degranulation and cytokine production in human MCs. Furthermore, a study of two patients with food allergy receiving ibrutinib for CLL suggested that, through inhibition of IgE-dependent basophil and MC activation, BTK antagonists may be able to block IgE-mediated allergic reactions to food and other allergens.[38] BTK inhibition has been

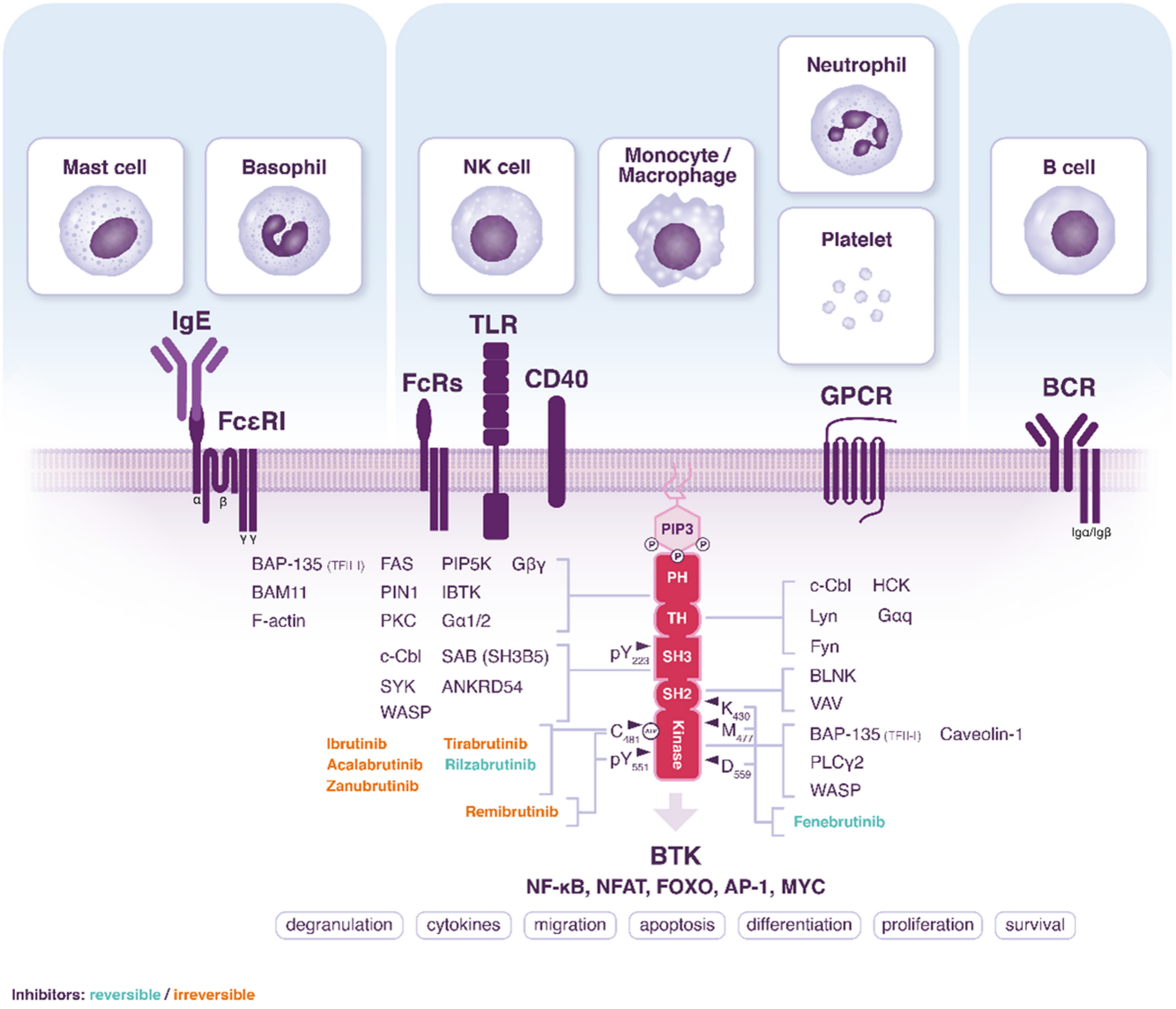

FIGURE 1 Role of BTK in immune cell signaling. The Tec-family kinase BTK is expressed in various cells including not only MCs and B cells but also NK cells, monocytes/macrophages, neutrophils, and platelets, where it functions as a major signaling element in diverse receptor signaling pathways. Upon receptor activation, BTK is recruited to the plasma membrane via interaction of its pleckstrin homology (PH) domain with phosphatidylinositol trisphosphate (PIP3). Phosphorylation at tyrosine Y551 by Src-family kinases triggers autophosphorylation at Y223 and the switch into the active conformation. This enables interaction with various downstream signaling and adapter molecules, leading subsequently to calcium release and activation of transcription factors such as NF-κB, NFAT, FOXO, AP-1, and MYC. In MCs and B cells, BTK signaling has been primarily—but not exclusively—connected to FcεRI and BCR signaling, respectively. BTK controls IgE-dependent MC activation and degranulation responses as well as B-cell survival and differentiation, thereby linking its activity to allergy and autoimmunity. BTK inhibitors are designed to specifically either covalently or reversibly target the active site of BTK, preventing ATP binding and stabilizing the inactive conformation. ANKRD54, ankyrin repeat domain 54; AP-1, activator protein-1; ATP, adenosine triphosphate; BCR, B-cell receptor; BLNK, B-cell linker protein; BTK, Bruton's tyrosine kinase; GPCR, G protein-coupled receptor; IBTK, inhibitor of Bruton's tyrosine kinase; IgE, immunoglobulin E; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; PH, pleckstrin homology; PIP5K, phosphatidylinositol 4-phosphate 5-kinase; PKC, protein kinase C; PLC, phospholipase C; SYK, spleen tyrosine kinase; TLR, toll-like receptor; WASP, Wiskott–Aldrich syndrome protein

shown to reduce a skin-prick test reaction to allergen in healthy adults with asymptomatic atopic diathesis in a Phase I trial.[39]

During IgE-mediated hypersensitivity reactions, activated MCs secrete preformed mediators such as histamine within minutes during the early-phase reaction, as well as rapidly synthesized lipid mediators such as leukotrienes and prostaglandins. Various cytokines and chemokines are subsequently generated a number of hours later during the late-phase response.[40] Passive cutaneous anaphylaxis experiments in mice have demonstrated that BTK regulates both early- and late-phase MC effector functions driven by FcεRI-mediated activation.[40] Indeed, BTK positively regulates almost any aspect of FcεRI-mediated MC function (with the exception

of interleukin-4 production, which is enhanced in the absence of BTK).[40] That BTK may also have negative regulatory roles is an important consideration; the use of BTK inhibitors for treatment of malignancies has not suggested a tendency for allergen sensitization, but the potential for this should be considered moving into treatment of immune-mediated conditions. A study in which MC activation was inhibited by the short-chain fatty acid, butyrate, suggested that MC activation relies on a strong transcriptional silencing of critical molecules for IgE receptor-induced signal transduction, including BTK.[41] Recent data have shown that—in contrast to FcεRI-mediated MC activation—stem cell factor-induced KIT signaling in bone-marrow-derived MC is largely independent of the phosphorylation and activation of BTK.[42]

2.2.3 | BTK signaling in other inflammatory responses

There is some evidence that BTK contributes to other inflammatory mechanisms, such as immunoglobulin G (IgG; FcγR)-mediated activation of monocytes and neutrophil migration.[43] For example, a study found that ibrutinib did not affect monocyte FcγR-mediated phagocytosis, even at supraphysiological concentrations, but suppressed FcγR-mediated cytokine production.[44] However, although ibrutinib blocked BTK in isolated cultures, pro-inflammatory intercellular communication was sufficient to overcome its inhibitory effects on monocytes and NK cells.[44] BTK-deficient neutrophils have shown defects in granulocyte-macrophage colony-stimulating factor (GM-CSF)-signaling and GM-CSF-induced maturation accompanied with impaired function during an acute inflammatory response.[15]

3 | BTK PATHWAY INHIBITION IN THE TREATMENT OF SKIN DISEASES

On the basis of the involvement of the BTK pathway in autoimmune, IgE-mediated allergic, and other inflammatory mechanisms, BTK inhibition is emerging as a candidate therapeutic approach for a number of dermatological disorders.

3.1 | Chronic spontaneous urticaria

CSU is defined by the presence of wheals and/or angioedema occurring for more than 6 weeks without a specific trigger.[45] It is a common condition, affecting approximately 1% of the population worldwide,[46] and showing an increasing trend over time.[47] The burden experienced by patients with CSU can be considerable, with challenges such as sleep deprivation, sexual dysfunction, limitations on daily life, and reduced performance at work or school all affecting health-related quality of life.[46] A lack of understanding of underlying cause has precluded development of curative treatments,[48] and patients often experience long delays in achieving effective management[46]; indeed, many patients do not achieve symptom control.[49] Fewer than half of the patients with CSU respond to a standard-dosed H1-antihistamine, the first-line recommended treatment.[50] The only other licensed treatment for CSU is the anti-IgE monoclonal antibody, omalizumab, which, in a phase 2 head-to-head trial, showed a complete hive response rate of 26%, compared with 30%–51% with the anti-IgE ligelizumab.[49] Agents such as cyclosporine, dapsone, and hydroxychloroquine are used off-label.[45] Novel treatment options with improved effectiveness are urgently needed for patients with CSU.

The rationale for BTK inhibition in CSU is strong, as BTK is involved in both of the known pathways that lead to the degranulation of skin MCs, the key pathogenic driver of CSU (Figure 2A). In type I (autoallergic) CSU, the occurrence of signs and symptoms is driven by IgE to autoallergens (e.g., against thyroperoxidase, thyroglobulin, tissue factor, interleukin-24, and double-stranded DNA), while type IIb autoimmune CSU is due to MC-targeted IgG autoantibodies against IgE or FcεRI.[51] Type IIb CSU is the less common endotype, but is characterized by high disease activity and poor response to treatment with antihistamines and omalizumab.[51–54]

BTK inhibitors have potential for efficacy in both autoallergic and autoimmune CSU due to inhibition of BTK-mediated degranulation in MCs and autoantibody production in B cells. In particular, they may help to address the suboptimal levels of response to currently available treatments in type IIb CSU.[52,53,55]

3.2 | Pemphigus

Pemphigus is an autoantibody-driven skin disease characterized by a loss of cell adhesion (acantholysis), leading to blisters or erosions of the skin and/or mucous membrane.[56,57] There are three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus; of these, pemphigus vulgaris is the most common variant.[56] The pathology of pemphigus is based on IgG autoantibodies targeting various adhesion molecules in the epidermis, including desmoglein (DSG) 1 and 3.[56] Dendritic cells presenting DSG antigens can activate T cells, in turn triggering anti-DSG antibody production from B cells (Figure 2B).[57]

The mainstay of pemphigus therapy is immunosuppression, primarily with systemic corticosteroids and rituximab. However, these agents can be associated with significant side effects; severe infection induced by an immunocompromised state is a major cause of death in patients with pemphigus.[58,59] Rituximab, while a very effective treatment option, requires intravenous administration and results in B-cell depletion, potentially contributing to a higher rate of severe infections. There is an unmet need for steroid-sparing agents with rapid onset, patient-friendly administration, and an acceptable safety profile, including lack of chronic B-cell depletion. Targeted approaches such as the use of engineered human cytotoxic chimeric autoantigen receptor (CAAR)-T cells to specifically kill B cells producing autoantibodies are under clinical investigation for pemphigus.[60] Given the key role of BTK in

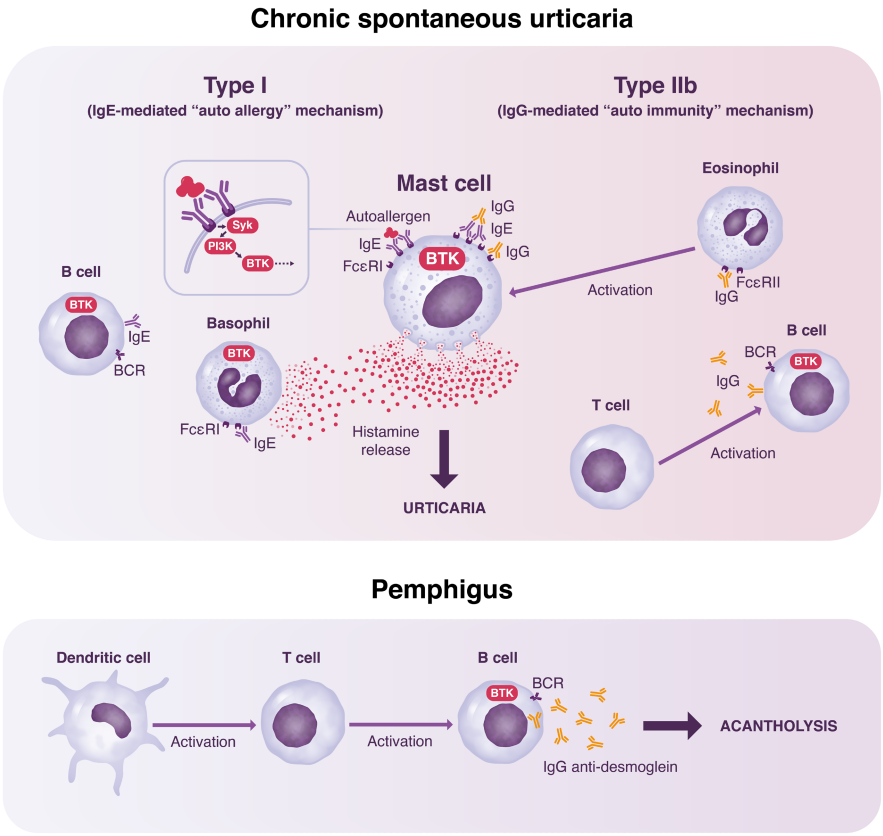

FIGURE 2 Overview of the role of BTK in the pathophysiology of (A) CSU and (B) pemphigus. BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IgG, immunoglobulin G. (A) CSU: The pathogenesis of CSU involves antibody-mediated MC and basophil activation, occurring via IgE ("auto allergic" or type I CSU) or IgG ("auto immune" or type IIb) generated by differentiated B cells. In type I CSU, crosslinking of FcεRI via autoreactive IgE molecules directed against self-antigens such as thyroid peroxidase promotes MC/basophil degranulation. In type IIb CSU, IgG molecules directed against the Fc portion of IgE or the FcεRI promote spontaneous cellular degranulation.[119] The role of eosinophils is debated, but eosinophil proteins may promote mast cell degranulation in CSU, and eosinopenia has been linked to high disease activity, type IIb autoimmunity, and poor response to treatment.[120] In addition to its well-established role in B-cell signaling, evidence suggests that BTK is specifically required for IgE-mediated activation of basophils[37] and in MC FcεRI-induced cytokine secretion.[121] (B) Pemphigus: Dendritic cells presenting desmoglein (DSG) antigens activate T cells, in turn triggering BTK-mediated anti-DSG antibody production from B cells[57]

the responses of autoreactive B cells, BTK inhibitors represent a promising therapeutic strategy for pemphigus.

3.3 | Other skin conditions

CSU and pemphigus are the focus of attention with respect to the potential of BTK inhibition for efficacy in dermatological conditions, but patients with other chronic inflammatory skin diseases, including hidradenitis suppurativa (HS), systemic lupus erythematosus (SLE), and atopic dermatitis can be expected to also benefit from this therapeutic approach.

HS is a chronic inflammatory skin disease, characterized by cutaneous inflamed nodules, abscesses, and pus-discharging tunnels developed in axillary, inguinal, gluteal, and perianal body sites.[61] Steroid injections, antibiotic creams, or oral antibiotics are first-line options used to treat HS; for moderate-to-severe and/or recalcitrant cases, anti-TNF treatment with adalimumab is currently the only approved therapy.[62] Surgery is necessary for some patients with HS, particularly when significant scarring has occurred.[63] The immunopathogenesis of HS is poorly understood, but B cells—particularly plasma cells—have been identified as a potential therapeutic target. Characterization of the inflammatory response in HS using proteomic and transcriptomic approaches has revealed enrichment of BTK signaling, thus supporting the potential value of BTK inhibition as a therapeutic strategy.[64]

SLE is a chronic autoimmune disease characterized by autoantibodies against nuclear antigens.[65] Cutaneous disease is a common manifestation of SLE; indeed, skin is the second most affected organ after articular involvement.[66] The disease is characterized by altered B-cell selection, triggering production of autoreactive antibodies and pro-inflammatory cytokines, and the presentation of autoantigens to autoreactive T cells.[65] Due to the heterogeneity in the etiopathogenesis of SLE, numerous therapeutic targets have been investigated,[67] but the first drug approved by the FDA for the treatment of SLE in over 50 years was belimumab, a fully human

IgG1 monoclonal antibody, which selectively targets and inhibits the B-cell survival factor, B-lymphocyte stimulator (BLyS).[68] Several components of BTK signaling pathways are altered in B cells from patients with SLE, and BTK is considered to be a promising therapeutic target for the treatment of cutaneous as well as CNS, renal, and articular manifestations of SLE.[65]

Atopic dermatitis is the most common inflammatory skin disease, characterized by impaired barrier function.[69] Current pharmacological management strategies include topical agents such as corticosteroids, calcineurin inhibitors and phosphodiesterase-4 inhibitors, and systemic agents including broad-spectrum immunosuppressants, cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine.[70] While BTK inhibition is one of a number of therapeutic strategies under investigation,[71] recent additions to the armamentarium include monoclonal antibodies (dupilumab and tralokinumab), along with Janus kinase inhibitors (baricitinib, upadacitinib and abrocitinib).[72] The penetration of antigens through the impaired dermatological barrier leads to production of cytokines such as thymic stromal lymphopoietin, which triggers BTK-dependent signaling and this may be of therapeutic interest.[69]

There may also be a role for BTK inhibitors in the treatment of pure IgE-mediated conditions such as anaphylaxis of IgE-mediated food allergy; further studies are warranted in this area.

4 | BTK INHIBITORS IN CLINICAL PRACTICE

4.1 | First-generation BTK inhibitors

Since ibrutinib came to the market in 2013 for the treatment of adult patients with MCL, its range of indications has expanded, and a number of other BTK inhibitors, such as acalabrutinib, zanubrutinib, and orelabrutinib, have been developed for the treatment of B-cell malignancies (Figure 1).[73–78] Acalabrutinib, for example, has demonstrated improved potency and selectivity, with reduced off-target side effects, compared with ibrutinib, while zanubrutinib is another selective BTK inhibitor with superior oral bioavailability and greater BTK specificity than ibrutinib.[79] All of these agents, however, interact with their target via covalent bonding, a feature which, while affording impressive efficacy, has also been associated with drug resistance and a challenging tolerability profile.[77] Aside from BTK, covalent agents may also bind to other kinases, including—but not limited to—those that feature, a cysteine at the same position as BTK.[76] Severe adverse events (AEs) associated with early BTK inhibitors include hemorrhage, hypertension, cardiac arrhythmias and cardiac failure, second primary malignancies, and tumor lysis syndrome.[80] Some of the most common AEs, occurring in more than 30% of patients, are thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.[80] As might be expected for a treatment that targets B cells, BTK-inhibitor therapy elevates the risk of infection.[80] Ibrutinib treatment is associated with an increased risk of pneumonia, sinusitis, and infections of the upper respiratory and urinary tracts, as well as opportunistic skin infections including herpes simplex and herpes zoster virus reactivations, and *Staphylococcus aureus* superinfection.[81] The precise role played by BTK in pathogenic microorganism infections is not yet clear and remains the subject of investigation.[82]

The risk-to-benefit profile of these early BTK inhibitors requires re-evaluation when considering their potential to offer therapeutic benefits outside of the oncology setting. An AE profile that is considered acceptable for the management of a life-threatening cancer is different from that which can reasonably be recommended for chronic treatment of conditions that considerably affect patients' quality of life but are not life-threatening. As seen above, there is a strong rationale for the potential benefits of BTK inhibitors in some autoimmune and allergic conditions. While agents such as acalabrutinib and zanubrutinib offered improvements over ibrutinib, supporting potential roles in treating chronic, non-malignant conditions such as food allergy or IgG4-related disease, a need for the efficacy of BTK inhibitors with an improved AE profile has seen a shift toward development and investigation of a new generation of drugs in this class.[76,83]

One strategy being used to address this is the use of BTK inhibitors that utilize non-covalent binding mechanisms.[77] An important benefit in the use of covalent inhibitors is their ability to achieve high, sustained occupancy of the target without the need for extended drug exposure.[76] However, non-covalent inhibitors may be able to overcome drug resistance, owing to a lack of dependence on binding to C481 mutations, which are a major mechanism for acquired resistance in oncologic indications.[77] Several non-covalent BTK inhibitors are in development for B-cell malignancies and, while longer-term studies are required, early clinical data suggest high levels of specificity and an improved tolerability profile.[77,84,85]

4.2 | Next-generation BTK inhibitors for dermatology/allergology indications

An overview of next-generation BTK inhibitors in development for immune-mediated dermatological indications is provided in Table 1 (also shown in Figure 1). Fenebrutinib (GDC-0853, RG7845) is a highly selective, reversible, non-covalent, oral BTK inhibitor.[86] Remibrutinib (LOU064), rilzabrutinib (PRN1008), and tirabrutinib (ONO/GS-4059) are all oral agents, which bind covalently to their BTK target but with high levels of selectivity.[83,87,88] In the case of remibrutinib, improved selectivity and tolerability are likely attributable to its ability to bind to an inactive conformation of BTK.[83] Rilzabrutinib demonstrates high affinity and selectivity for the BTK receptor, combined with a long duration of action due to prolonged, but reversible, target occupancy.[87] Tirabrutinib binds in an irreversible covalent manner. High specificity of tirabrutinib binding to C481 on the BTK active site has been confirmed experimentally via mass spectrometry.[89]

TABLE 1 BTK inhibitors in development (phase II+) for treatment of immune-mediated dermatological diseases

Drug	Other names	Manufacturer/developer	Indication	Phase	Trial identifier (status)
Branebrutinib	BMS-986195	Bristol–Myers Squibb	Atopic dermatitis	II	NCT05014438 (recruiting)
			SLE[a]	II	NCT04186871 (recruiting)
Fenebrutinib	GDC-0853	Genentech	CSU	II	NCT03137069 (completed)
				II	NCT03693625 (terminated)
			SLE	II	NCT02908100 (completed)
Remibrutinib	LOU064	Novartis	CSU	II	NCT03926611 (completed)
				II	NCT04109313 (active, not recruiting)
				III	NCT05030311/ NCT05032157 (not yet recruiting)
				III	NCT05048342 (not yet recruiting)
Rilzabrutinib	PRN1008	Principia Biopharma/Sanofi	Pemphigus vulgaris	II	NCT02704429 (completed)
				III	NCT03762265 (active, not recruiting)
			IgG4-related disease	II	NCT04520451 (recruiting)
			Atopic dermatitis	II	NCT05018806 (recruiting)
Tirabrutinib	GS-4059	Gilead	CSU	II	NCT04827589 (withdrawn)
			Pemphigus	II	JapicCTI-184231

Note: Trial identifier and status information taken from clinicaltrials.gov, with the exception of JapicCTI-184231 (NIPH Clinical Trials Search at https://rctportal.niph.go.jp/en)

Abbreviations: CSU, chronic spontaneous urticaria; SLE, systemic lupus erythematosus.

[a]In addition to autoimmune disorder, rheumatoid arthritis and primary Sjögren's syndrome.

4.3 | Clinical development of BTK inhibitors for the treatment of chronic inflammatory skin diseases

In the fields of dermatology and allergology, CSU is a focus of particular interest for the development of next-generation BTK inhibitors. Remibrutinib and fenebrutinib are most advanced in their clinical development for CSU, both with phase II studies completed.

The first-in-human study of remibrutinib (in healthy and asymptomatic atopic volunteers; NCT03918980) demonstrated a very fast onset of action and full BTK occupancy for at least 24 h following single doses of 30 mg and higher, while repeated dosing did not cause accumulation.[39] Near-complete inhibition of blood basophil degranulation was achieved with doses of at least 50 mg.[39,90] A phase II study of remibrutinib and an open-label extension study have been initiated in CSU: initial data from the dose-finding study in 311 patients with CSU inadequately controlled by H1 antihistamines (NCT03926611) indicated that all tested remibrutinib doses provided significant improvements in urticaria activity score (UAS7) change from baseline at Week 4 and Week 12 compared with placebo, supported by a favorable safety profile.[91,92] The open-label, multicenter, extension study (NCT04109313) is ongoing to evaluate the long-term safety and tolerability of remibrutinib in eligible patients with CSU; this has enrolled 195 participants and is due to complete in late 2022.[93] Phase III trials of remibrutinib for CSU inadequately controlled by H1 antihistamines are planned to initiate late in 2021 (NCT05030311, NCT05032157, and an open-label study in Japan: NCT05048342).[94,95] Also of note in the context of atopic disease, the first-in-human study of remibrutinib demonstrated a dose-dependent reduction in wheal size in skin-prick tests in individuals with atopic diathesis or atopic dermatitis.[39,90]

Following a phase I study investigating a single, oral dose of fenebrutinib in healthy volunteers (NCT03596632),[96] two phase II trials of fenebrutinib have been initiated in patients with CSU. In a double-blind, placebo-controlled trial in 93 adults with CSU refractory to antihistamines (NCT03137069), fenebrutinib was associated with significant improvements from baseline in UAS7 over 7 days at week 8 (primary endpoint) at doses of 150 mg daily and 200 mg twice daily.[97] Patients with type IIb autoimmunity were apparently more responsive to lower doses of fenebrutinib than those without autoimmunity, and fenebrutinib substantially reduced IgG-anti-FcεRI relative to baseline.[97] Numbers of AEs were generally balanced across fenebrutinib and placebo groups and were mild or moderate in severity. Transient grade 3 elevations in alanine transaminase were noted with fenebrutinib 150 mg daily and 200 mg twice daily. Two serious AEs considered to be related to treatment were reported in the 200 mg twice-daily fenebrutinib arm (periorbital cellulitis and an increase in hepatic enzymes), and led to treatment withdrawal.[97] The second, phase II study was an open-label, multicenter extension of

the double-blind trial, designed to evaluate the long-term safety and efficacy of fenebrutinib in patients with CSU.[98] This extension study was terminated following an interim analysis of data from the parent study.[98] Fenebrutinib (150 mg daily or 200 mg twice daily) was also evaluated in a placebo-controlled, phase II trial in patients with SLE (NCT02908100); it demonstrated evidence of strong pathway inhibition (reduced BTK-dependent plasmablast RNA signature, anti-dsDNA autoantibodies, total IgG and IgM, and increased complement C4, versus placebo), although the trial's primary endpoint (SLE Responder Index-4 at week 48) was not met.[99] Safety results were similar across all arms, except that serious AEs were more frequent with 200 mg twice-daily fenebrutinib. More AEs led to treatment withdrawal in the fenebrutinib 200 mg twice-daily group (19%; $n = 17$) than in the fenebrutinib 150 mg once daily group (8%; $n = 7$) or placebo group (8%; $n = 7$). The most common reason for discontinuation was lymphopenia ($n = 1$ and $n = 3$ in the 150 mg daily and 200 mg twice-daily arms, respectively; $n = 0$ in the placebo arm).[99]

In addition to these two "front runners," other agents are in development for immune-mediated dermatological conditions. Rilzabrutinib has been investigated in the multicenter, proof-of-concept, phase II, BELIEVE study in 27 patents with moderate and moderate-to-severe pemphigus vulgaris.[100] Rilzabrutinib is being studied further in the pivotal, phase III, PEGASUS trial (131 patients with pemphigus vulgaris or pemphigus foliaceus have been enrolled worldwide); this trial did not meet its primary or key secondary endpoints.[101,102] Tirabrutinib is already approved for recurrent or refractory primary central nervous system lymphoma and under regulatory review for WM and lymphoplasmacytic lymphoma in Japan, and is in clinical development in Japan for pemphigus.[88,103] Patients are currently being recruited for phase II trials of branebrutinib: one in atopic dermatitis and the second in a range of conditions including SLE.[104,105]

4.4 | The potential of BTK inhibitors to address unmet clinical needs in dermatology

Recent years have seen a number of therapeutic advances in immune-mediated dermatological conditions such as CSU or pemphigus and also in SLE. The availability of monoclonal antibodies for the treatment of these conditions (e.g., omalizumab, rituximab, and belimumab, respectively[106–108]) is a particularly exciting prospect. These biologic agents are, nonetheless, associated with limitations, such that important unmet needs remain in the management of these diseases.

Firstly, nearly a third of patients with CSU remain symptomatic when receiving licensed doses of omalizumab, even after 6 months of treatment.[109] Strategies such as updosing and biomarker profiling are being investigated to try and improve the rate of clinical response.[109,110] The second limitation relates to the route of administration of the monoclonal antibody treatments. Those administered subcutaneously require training in self-administration from a healthcare professional, while treatments administered intravenously are associated with considerable healthcare resource burden as dosing must be carried out in a hospital setting. In terms of mode of action, biologic treatments target one specific molecule. For conditions such as CSU or SLE with multifactorial pathogenesis, this may not be the optimal therapeutic approach. It is also important to consider the tolerability profiles of these biologic agents. The safety profile of omalizumab is generally considered highly favorable, although it demonstrated an increased frequency of mild-to-moderate AEs, which were mainly upper respiratory tract infections, compared with placebo in clinical trials.[111] Rituximab is generally well tolerated, but treatment is associated with a rare, yet important, risk of infusion-related reactions.[112] Moreover, there is also a risk of severe infections during rituximab treatment, which may be fatal.[113] Belimumab, which has been shown to improve mucocutaneous manifestations of SLE,[114] demonstrated a similar overall rate of AEs as placebo in SLE clinical trials.[115] However, it has also been associated with a risk of rare but severe AEs such as serious infections, neoplasms, and progressive multifocal leukoencephalopathy.[115]

Drugs that target inhibition of the BTK pathway represent a new therapeutic approach for patients with immune-mediated dermatological conditions and have the potential to address previously unmet needs. In contrast to monoclonal antibody treatments, these agents feature oral administration (although requiring more frequent dosing, so the likely impact on adherence is unclear) and a favorable mechanism of action that targets a significant pathogenic pathway rather than a single molecule. BTK inhibitors do not carry the safety concerns that have been associated with the biologic treatment options.

Generally speaking, across the immune-mediated diseases market, small molecules are more accessible than biologics due to disparities in their science, production strategies, and existing government policies.[116] However, pharmacoeconomical comparisons should be informed by other aspects such as efficacy, safety, direct, and indirect health and societal costs of treating chronic inflammatory diseases. Regarding diseases such as CSU or pemphigus, small molecules such as BTK inhibitors are entering a space already populated with approved biologic therapies, and only time can tell how this market will evolve.

It is also worth considering that BTK inhibitors may prove a useful tool to address gaps in understanding of the functions of MCs, basophils, and B cells, and their roles in the pathogenesis of skin diseases.[117] For example, research with ibrutinib using the chronic urticaria–basophil activation test (CU-BAT) has helped to show that the IgE/FcεRI-BTK pathway is dominant for the degranulation of basophils treated with sera of patients with autoimmune CSU, but that its inhibition does not completely abrogate basophil activation in all patients.[118]

5 | CONCLUSIONS

The development of treatments for immune-mediated dermatological conditions presents a particular challenge: A successful therapy not only must be effective but also boast a tolerability profile that

is acceptable for the long-term treatment of a chronic condition that affects quality of life but does not significantly reduce life expectancy. BTK inhibitors present themselves as promising candidates for this role. The wide-ranging clinical potential of BTK inhibition is based on the involvement of BTK in various inflammatory mechanisms and in the pathogenesis of many immunological disorders. Somewhat paradoxically, BTK inhibitors may also offer high levels of specificity with improved tolerability versus existing treatment options, owing to reduced off-target activity. There is currently a focus on development of these agents in CSU and pemphigus, but they also have potential in SLE and other allergic/autoimmune disorders. In addition to inhibition of FcεRI signaling in MCs and basophils, other effects such as blocking of BCR signaling and disruption of autoantibody production may contribute to the efficacy of these agents and are worthy of further study.

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CONFLICTS OF INTEREST

PM-B received honoraria for acting as a consultant and/or as a speaker for AbbVie, Janssen, Novartis, LEO Pharma, Almirall, Sanofi, Viatris, L'Oréal, and Cantabria Labs and served as a principal investigator in clinical trials supported by AbbVie, Sanofi, and Novartis. AB received honoraria for lectures and educational events for LEO Pharma, Janssen-Cilag, AbbVie, and Novartis. PK received payment/honoraria for lectures/presentations outside of submitted work for Novartis and Roche.. SM-R received funding from GA²LEN Global Allergy and Asthma European Network. MM served as a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Blueprint, Celldex, Centogene, CSL Behring, FAES, Genentech, Gilead, GIInnovation, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third Harmonic Bio, UCB, and Uriach. SF and JS have no conflicts of interest to disclose.

ORCID

Pedro Mendes-Bastos https://orcid.org/0000-0002-2439-920X
Ana Brasileiro https://orcid.org/0000-0002-8359-6561
Pavel Kolkhir https://orcid.org/0000-0001-5380-8132
Stefan Frischbutter https://orcid.org/0000-0003-3971-7343
Sherezade Moñino-Romero https://orcid.org/0000-0003-3775-2989
Marcus Maurer https://orcid.org/0000-0002-4121-481X

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