



Opinion Article

Bruton's Tyrosine Kinase (BTK) Inhibitors: A New Therapeutic Frontier in Dermatology



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Clinical interest in Bruton tyrosine kinase inhibitors (BTKi) has undergone a notable shift in recent years. Although their development was initially consolidated in hematology, where they represented a decisive advance in diseases such as chronic lymphocytic leukemia,¹ we are now observing an increasing approach of these molecules to the field of immunologic dermatology. This shift reflects not only improved understanding of the role of BTK in B-cell activation,² but also its essential function in mast cells and basophils,^{3,4} key actors in multiple inflammatory dermatoses.

This emerging scenario invites critical reflection. New-generation BTKi present selectivity and safety profiles that differ substantially from those of drugs used in hematology, opening the door to therapeutic applications that could modify currently well-established strategies in dermatology (Table 1).

BTK is a cytoplasmic enzyme selectively expressed in various immune cells (macrophages, mast cells, basophils, platelets, and B cells), but absent in mature plasma cells and T lymphocytes.⁵ Its activation begins when BTK is recruited to the plasma membrane through its pleckstrin homology (PH) domain, allowing phosphorylation and functional activation. At this stage it is phosphorylated at the Tyr551 residue by kinases of the SYK and SRC families, subsequently leading to autophosphorylation at Tyr223.⁶ This process enables full activation of the enzyme. BTK plays a key role in signal transduction from the B-cell antigen receptor (BCR) and Fc receptors that activate IgG and IgE (FcγR, FcεR) in macrophages and mast cells, representing a central component of innate⁷ and adaptive immunity.⁸

The kinase domain of BTK contains a cysteine residue at position 481 (C481), shared with 11 other structurally related kinases. These include several members of the TEC family (BMX [bone marrow tyrosine kinase on chromosome X], TEC [tyrosine-protein kinase TEC], ITK [IL-2-inducible T-cell kinase], and TXK [also known as RLK, resting lymphocyte kinase]), as well as other kinases with relevant functions in cellular signaling (EGFR [epidermal growth factor receptor], ERBB2 and ERBB4 [ERBB family receptors involved in proliferative pathways], JAK3 [Janus kinase 3, key in cytokine signaling], BLK [B-lymphoid kinase, expressed in B cells], and MKK7 [MAP kinase kinase 7]).⁹ These conserved cysteines have been exploited to develop covalent inhibitors

targeting BTK, EGFR, JAK3, and MKK7. Selective covalent inhibitors allow prolonged inhibition of BTK despite reduced systemic exposure,¹⁰ a pharmacological property that may favor both sustained efficacy and improved tolerability¹¹ in the chronic treatment of immune-mediated dermatologic diseases.

In chronic spontaneous urticaria (CSU), the BTK target acquires particular relevance due to its central role in mast cell activation through the FcεRI receptor.¹² Inhibition of this pathway translates into rapid reduction of pruritus and urticarial activity (wheals), an effect consistently demonstrated in clinical trials with remibrutinib. In phase II and phase III clinical trials,¹³ the drug has shown efficacy even in patients previously unresponsive to omalizumab,¹⁴ a clinically challenging subgroup often associated with mechanisms less dependent on IgE. The observation that remibrutinib maintains efficacy independently of FcεRI expression or previous anti-IgE response reinforces its potential utility in CSU phenotypes with type IIB autoimmunity.

In our view, this finding is particularly relevant because it positions remibrutinib as a therapeutic option capable of filling a gap in the current treatment algorithm: patients with CSU in whom elevated total IgE is not the main driver of disease. In these forms, BTK inhibition offers a more direct approach by blocking mast cell activation upstream and independently of the degree of IgE sensitization. Considering these data, and from a clinical perspective, it is reasonable to anticipate that remibrutinib could become a first systemic therapy option in patients without a clearly "IgE-dependent" phenotype. Factors such as the individual patient profile, the desired speed of response, dosing convenience, and the final cost of treatment will determine its precise position within the algorithm; nevertheless, its selective mechanism, rapid onset of action, demonstrated efficacy in biologic-refractory patients, and clearly favorable safety profile in clinical trials¹⁵ suggest that BTK inhibitors could significantly redefine the therapeutic approach to CSU in the coming years. In addition, research with remibrutinib is being extended to the adolescent population (12–18 years, NCT05677451), suggesting a possible future role at earlier stages of disease and in early treatment strategies.

Rilzabrutinib is a reversible covalent BTK inhibitor designed to bind the Cys481 residue with high affinity while allowing subsequent dissociation. This mechanism distinguishes it from remibrutinib, whose covalent bond is irreversible. In CSU, rilzabrutinib has been evaluated in patients who remained symptomatic despite the use of second-

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Table 1

Classification of BTK inhibitors and current status of their clinical development in dermatology. The main compounds under investigation, their mechanisms of action, and the dermatologic areas in which they are being evaluated are shown. Information on ongoing studies (identified by NCT numbers) was obtained from the public database ClinicalTrials.gov.²⁹

Classification of BTK inhibitor	Mechanism of action	Representative drugs	Areas of research/clinical development in dermatology
1st generation (irreversible covalent, low selectivity)	Irreversible covalent binding to the Cys481 residue with off-target inhibition (TEC, EGFR).	Ibrutinib	No development in dermatology. An isolated case of improvement of paraneoplastic PV after initiation of ibrutinib has been reported. ²⁹
2nd generation – Hematology (irreversible covalent)	Greater selectivity than first-generation inhibitors; same binding to Cys481.	Acalabrutinib, zanubrutinib	No studies in dermatology.
Highly selective BTKi for dermatology			
Irreversible covalent	High affinity for Cys481 with minimal inhibition of other kinases.	Remibrutinib (Rhapsido™)	Chronic spontaneous urticaria: phase II–III (REMIX 1/2: NCT05030311, NCT05032157). Comparison with dupilumab in CSU: RECLAIM (NCT06868212). CSU in adolescents: NCT05677451. Inducible urticarias: NCT05976243. Hidradenitis suppurativa: phase III (RECHARGE-1: NCT06799000; RECHARGE-2: NCT06840392). CSU: RILECSU (NCT05107115).
Reversible covalent	Reversible binding to the Cys481 residue, with sustained inhibition and reduced off-target effects.	Rilzabrutinib (PRN1008) and PRN473 (topical)	AD: phase II (NCT05018806; rapid reduction of pruritus, EASI endpoint not achieved). PV: phase II; phase III PEGASUS completed.
Reversible non-covalent	Reversible binding to the ATP pocket without interaction with Cys481.	Fenebrutinib (GDC-0853)	CSU: phase II (NCT03926611) → clinical development discontinued.
TEC family/JAK3 inhibitors (not classical BTKi)	Inhibition of JAK3, TEC, ITK, and RLK → modulation of T and NK lymphocytes.	Ritlecitinib (Litfulo™)	AA: approved in 2023 (FDA and EMA) in adolescents ≥12 years of age.

BTK: Bruton tyrosine kinase; BTKi: Bruton tyrosine kinase inhibitor; Cys481: cysteine residue 481 in the BTK kinase domain; CSU/UCE: chronic spontaneous urticaria; HS: hidradenitis suppurativa; AD: atopic dermatitis; PV: pemphigus vulgaris; AA: alopecia areata; TEC: Tec family tyrosine kinases, including BTK, TEC, ITK, and RLK; ITK: IL-2–inducible T-cell kinase; RLK: resting lymphocyte kinase; JAK3: Janus kinase 3; ATP: adenosine triphosphate.

generation antihistamines (RILECSU study, NCT05107115).¹⁶ These preliminary data support interest in BTK modulation through reversible approaches complementary to irreversible covalent inhibitors and open the possibility that different inhibition profiles may be better suited to particular clinical subgroups within the disease. In moderate-to-severe atopic dermatitis, a phase II trial of rilzabrutinib¹⁷ did not meet the primary endpoint of improvement in EASI, although it did show rapid and consistent reduction in pruritus with a very favorable safety profile, suggesting a potential role in phenotypes with pruritus refractory to other targeted therapies. In pemphigus vulgaris, the phase II BELIEVE study showed that rilzabrutinib was able to induce rapid disease control with reduced corticosteroid doses and a favorable toxicity profile,¹⁸ maintaining adequate tolerability even during prolonged treatment. Although the trial did not reach its primary endpoint, the magnitude and consistency of the clinical response, together with improvement in disease activity parameters and reduction in corticosteroid requirements, maintain interest in this target as a potentially relevant corticosteroid-sparing strategy in certain variants or evolutionary stages of the disease.¹⁹

Interest in BTK inhibitors in hidradenitis suppurativa (HS) is supported by emerging evidence indicating an important role for B cells and plasma cells in the chronic inflammatory process of the disease.²⁰ Several studies have shown that these lymphocytes may represent up to 20% of the inflammatory infiltrate in lesions and organize into tertiary lymphoid structures, participating in local autoantibody production and activation of BTK- and SYK-dependent pathways.²¹ Although clinical trial results with BTKi in HS have not yet been published, 2 phase III clinical trials on remibrutinib (RECHARGE 1 and 2) have been initiated,^{22,23} reflecting growing interest in this target in the disease. BTKi

could offer advantages such as oral administration, specific inhibition of pathogenic pathways, and a favorable safety profile.

Finally, although alopecia areata (AA) has not been directly evaluated with classical BTK inhibitors, the importance of the TEC family, to which BTK belongs, is demonstrated by ritlecitinib, a selective JAK3/TEC inhibitor recently approved for the management of AA in adolescents aged 12 years and older.²⁴ Its clinical efficacy confirms the relevance of this pathway in the modulation of follicular immunity and reinforces the biological plausibility of directing selective oral therapies toward the BTK/TEC pathway in other autoimmune skin diseases.

Adverse effects associated with BTK inhibitors used in hematology have been a subject of debate since the introduction of ibrutinib, whose limited selectivity has been linked to cardiovascular events (atrial fibrillation), hemorrhagic complications, and GI toxicity.²⁵ In the context of refractory hematologic malignancies, these risks may be acceptable given the severity of disease and the need for effective therapeutic options. In dermatology, however, we face chronic conditions requiring prolonged and well-tolerated treatments, where the threshold for acceptable adverse effects is necessarily different.

In this regard, BTK inhibitors specifically developed for immune-mediated diseases present a markedly more favorable safety profile. Remibrutinib has shown adverse event rates comparable to placebo in phase II and phase III clinical trials,¹⁴ without increased cardiovascular events, bleeding, or severe infections. Furthermore, rilzabrutinib has demonstrated excellent tolerability, with adverse effects mainly mild and limited to the GI domain.²⁶ This difference in safety appears to be directly related to their high selectivity for BTK and the minimization of off-target inhibition of kinases such as TEC or EGFR, responsible for much of the toxicity associated with first-generation BTKi.

From a clinical perspective, we consider that this “cleaner” safety profile is one of the strongest arguments supporting the integration of BTKi into dermatology. The combination of rapid efficacy, pharmacodynamic stability, and good tolerability makes them particularly attractive candidates for chronic inflammatory skin diseases requiring continuous treatment. Nevertheless, long-term pharmacovigilance data and real-world experience will be essential to define precisely which patients benefit most and how this therapeutic class should be positioned within treatment algorithms.

Beyond the indications currently under investigation, BTK inhibitors could have an emerging role in the management of chronic mast cell-dependent pruritus, particularly in patients with pruritus of unknown origin or refractory to conventional treatments.²⁷ Selective modulation of the BTK–SYK pathway affects pruritic pathways that are not exclusively histaminergic, opening the door to future proof-of-concept studies in these phenotypes, where therapeutic alternatives remain limited.²⁸

Overall, BTK inhibitors are one of the most promising therapeutic approaches in dermatology. Their rapid action, IgE-independent mechanism, and favorable safety profile position them as strong candidates to expand the therapeutic arsenal in several inflammatory dermatoses. As ongoing clinical trials mature, BTKi are likely to acquire an important – and possibly preferred – role in certain phenotypes within therapeutic algorithms, offering effective and well-tolerated alternatives for patients with unmet needs.

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