doi:10.36849/JDD.2024.NVRN0824

NEWS, VIEWS, & REVIEWS

Applications of Bruton Tyrosine Kinase Inhibitors in Dermatology

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INTRODUCTION

A member of the tyrosine-protein kinase Tec (TEC) family of tyrosine kinases, Bruton's tyrosine kinase (BTK) is a cytoplasmic, nonreceptor kinase essential to myriad immunological pathways.[1] Activity of BTK most notably underlies B cell development, migration, and activation through B cell receptor (BCR) activation.[1] BTK is also critical for its role in receptor-mediated signal transduction of Fc receptors, toll-like receptors (TLRs), and chemokine receptors.[1] For its dual activity in both adaptive and innate immunity, inhibition of BTK is a potential therapeutic target for autoimmune and allergic dermatologic diseases.[2,3] Emerging applications of BTK-inhibiting drugs in dermatology will be reviewed herein, with a focus on chronic spontaneous urticaria (CSU) and pemphigus vulgaris (PV).

Mechanism of Action

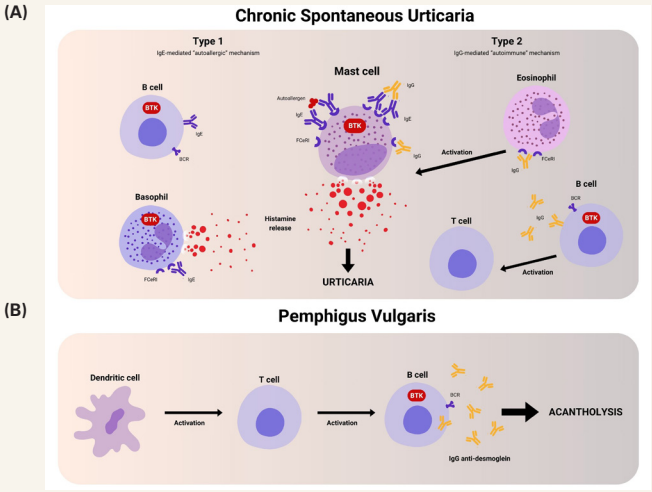
The first-in-class BTK inhibitor, ibrutinib, arrests the enzymatic activity of BTK by forming a covalent, irreversible bond to the cysteine residue C481 of the kinase domain. By preventing downstream activation of BCR pathways, B cell growth, proliferation, and survival is halted. Although effective for the treatment of several lymphoproliferative disorders, ibrutinib inhibits other kinases causing several concerning adverse effects; the development of mutations conferring resistance to ibrutinib is also an arising problem.[1]

Second-generation BTK inhibitors such as acalabrutinib and zanubrutinib also bind irreversibly and covalently to C481 but with higher selectivity, exhibiting less off-target toxicities than ibrutinib.[1,4] To further limit undesired toxicities and resistance, next-generation BTK inhibitors utilize novel mechanisms, such as employing reversible inhibition and targeting alternative binding sites, thus expanding their clinical potential to treat chronic, non-oncological conditions.[1,4]

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is a common and increasingly prevalent condition worldwide that imparts a profound burden on patient quality of life.[5,6] For patients with disease inadequately controlled using first-line H1-antihistamines then anti-IgE monoclonal antibody biologic therapies, BTK inhibition is an emerging yet currently off-label treatment strategy as its activity is essential to the IgE-mediated activation of human mast cells and basophils underlying CSU.[3] Through BTK inhibition, the signal cascade initiated by cross-linking of the high-affinity receptor FcεRI is arrested, preventing subsequent cellular degranulation, leukotriene and prostaglandin production, and cytokine synthesis.[3] Currently two distinct pathophysiologic mechanisms promoting mast cell (MC) activation in CSU are recognized: type 1 (autoallergic) mediated by IgE molecules directed against self-antigens, and type IIb (autoimmune) mediated through IgG molecules directed against the Fc region of IgE or the FcεRI (Figure 1A).[7] Although less common, type IIb CSU is associated with more severe disease and poor response to H1-antihistamines and omalizumab.[7,8] With the ability to address both IgE- and B cell-mediated sources of MC degranulation, BTK inhibitors have the potential for greater efficacy than currently available treatments for CSU, even the more treatment-resistant autoimmune type.[7]

Figure 1. Role of BTK in the pathophysiology of CSU and pemphigus. Figure adapted from Mendes-Bastos et al.[2] **(A)** CSU: Mast cell degranulation is the key pathogenic driver of CSU, with two pathogenic endotypes accepted: type 1 CSU (autoallergic) due to crosslinking of FcεRI via IgE directed at autoallergens, and type IIb CSU (autoimmune) due to IgG directed at the Fc region of IgE or the FcεRI. Eosinophils may also promote MC degranulation. BTK is required for IgE-mediated activation of basophils and FcεRI-initiated cytokine secretion. **(B)** Pemphigus: Presentation of desmoglien antigens by dendritic cells activates T cells thus inducing BTK-mediated anti-desmoglien antibody production by B cells. BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IgG, immunoglobulin G.



Several clinical trials are investigating three new generation BTK inhibitors as potential therapies for CSU refractory to antihistamines.[3] Remibrutinib, an oral BTK inhibitor drug, is

leading in development with two global, double-blind, placebo-controlled phase 3 trials (REMIX-1 and REMIX-2) completed and awaiting final analyses of results. Primary pooled analyses of the parallel trials (2:1 randomization; remibrutinib 25 mg twice-daily n=613 for up to 52 weeks; placebo n=312 for up to 24 weeks) found both primary endpoints met by achieving superior improvements vs placebo across three disease severity scores as early as week 2 and revealed favorable safety profiles.[9] Further analysis found remibrutinib remained efficacious vs placebo independent of prior exposure to anti-IgE biologic therapies.[10] Another selective BTK inhibitor, fenebrutinib, also demonstrated efficacy in treating antihistamine-refractory CSU in a phase 2a trial and notably showed reductions in autoantibody titers in patients with autoimmune disease; however, further development of fenebrutinib has been halted due to transient elevation of liver transaminases in these trials.[11-13] A final next-generation BTK inhibitor, rilzabrutinib, showed promise as an effective treatment for CSU in phase 2 trials although with a greater incidence of non-life threatening adverse effects compared to placebo.[14]

Pemphigus Vulgaris

Management of moderate to severe PV flares typically involves high-dose systemic corticosteroids and/or intravenous rituximab. While PV is primarily mediated by B cell and plasma cell autoantibodies against desmoglein antigens, activation of the innate immune system plays a role in pathogenesis (Figure 1B); thus, optimal therapeutic regimens should target both innate and active immunological pathways.[15] Rilzabrutinab imparts a favorable mechanism of action by targeting both pathways without directly affecting T cells or depleting B cells. In the phase II BELIEVE study which involved 27 patients with newly diagnosed or relapsing, mild-severe PV, control of disease activity with 400-600 mg twice daily rilzabrutinab monotherapy or concurrent low-dose corticosteroids was achieved in 52% of patients after 12 weeks.[15] At the 24-week follow-up, 22% of patients achieved complete remission, providing compelling evidence in support of rilzabrutinab's rapid clinical efficacy. Notably, treatment-related adverse events were largely mild-moderate, though 3 patients with complex medical histories experienced serious adverse events including cellulitis and pneumonitis. Part B of this trial confirmed and expanded on previous findings by implementing 24 weeks of treatment and more dosing options.[16] By week 4, 60% of patients demonstrated control of disease activity (n=15). Complete healing of all lesions and absence of new lesions was achieved in 40% of patients who were concurrently on low-dose corticosteroids on at least one visit. Thirteen patients experienced mild-moderate, transient treatment-emergent adverse events. Treatment failure was observed in one patient, who discontinued the study.

Additional Applications

BTK inhibition is also actively being investigated in clinical trials for the treatment of atopic dermatitis[3] and systemic lupus erythematosus,[13] and may be a future therapeutic strategy for the treatment of hidradenitis suppurativa given B cells and plasma cells are key pathogenic players in this disease.[17]

CONCLUSION

BTK inhibition is an emerging strategy for allergic and autoimmune dermatologic diseases. Advances in drug design have propelled BTK inhibition from being a solely oncologic therapy with severe side effects to a potentially pivotal treatment strategy in dermatology.

DISCLOSURE

CW's work is funded through an independent fellowship grant from Galderma; SAA's work is funded through independent fellowship grants from Lilly and Pfizer.

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