JOURNAL OF WOMEN MEDICAL & DENTAL COLLEGE

Bruton's Tyrosine Kinase Inhibitors in Chronic Spontaneous Urticaria: Unraveling Mechanisms, Clinical Efficacy, and Future Perspectives

Zainab Abdul Hamid[1]*, Afsheen Azhar[1], Naveed Ahmad[3], Rahat Ullah[2], Umaima[1], Muhammad Yousaf [2], Bahar Ullah[4], Safi Ullah Khan[5], Nighat Aziz [2]

[1] Dubai Medical University, Dubai, United Arab Emirates
[2] Gomal Medical College, Dera Ismail Khan, Khyber Pakhtunkhwa, Pakistan
[3] Khyber Medical College, Peshawar, Khyber Pakhtunkhwa, Pakistan
[4] Saidu Medical College, Swat, Khyber Pakhtunkhwa, Pakistan
[5] Bahria University Medical and Dental College, Karachi, Pakistan

Received date: 21-04-2026 **Publication date:** 30-04-2026

Abstract

Chronic spontaneous urticaria (CSU) is an inflammatory process that is mediated by mast cells, and that is characterized by the presence of recurrent wheals or angioedema or both over a period of more than six weeks. Antihistamines and biologic agents, including Omalizumab, have been available, but still a certain number of patients turn out to be resistant, and that is why it is necessary to find new targeted therapies. A promising target is Bruton tyrosine kinase (BTK), a central mediator of Fc5 receptor (Fc 5) signaling in mast cells and basophils. This narrative review included a collection of evidence about BTK inhibitors in CSU. PubMed and Google Scholar were searched in a structured manner covering up to February 2026. Randomized controlled trials, early-phase clinical trials, observational studies, and mechanistic studies evaluating the BTK inhibitors in CSU were all included in the search. Compilation of the results was done in a descriptive manner lacking a risk-of-bias evaluation. Preliminary clinical trials have demonstrated that specific BTK inhibitors, including remibrutinib and rilzabrutinib, cause quick decreases in the urticaria activity rating, enhance the symptoms and have favorable safety profiles in the short-term. BTK inhibition has been confirmed as a useful treatment in mechanistic studies to inhibit mast cell and basophil cell activation, thus preventing IgE-mediated and autoantibody-driven pathways that cause CSU. Initial findings suggest that there is a significant improvement in the patients who are antihistamine-resistant, but the long-term safety and maintenance of the response rates remain to be explored. BTK inhibitors are an encouraging new therapy in the treatment of CSU. Phase III trials and real-world investigations in the future will assist to establish their long-term effectiveness, safety, and place in the present treatment guidelines. This Review sets out to incorporate the current literature on the use of Bruton tyrosine kinase inhibitors in chronic spontaneous urticarcia.

Keywords Bruton Tyrosine Inase Inhibitors, Chronic Spontaneous Urticaria, Targeted Therapy, Remibrutinib, Rilzabrutinib

1. Introduction

Chronic spontaneous urticaria (CSU) represents a long-lasting inflammatory dermatological disorder, manifested by repetitive episodes of whealing, angioedema, or both for more than six weeks without an identifiable cause (1). Chronic spontaneous urticaria carries a substantial burden of disease, substantially impairing patients' quality of life, functionality, and associated with significant healthcare costs (2).

CSU may affect up to 1% of the general population, more frequently occurring in women, aged between 20 and 40 years (1, 3). From the pathophysiological point of view, CSU is associated with activation of mast cells

Corresponding author at: Zainab Abdul Hamid
Email address: zah20210165@gmail.com

https://doi.org/10.56600/jwmdc.v4i1.145

and basophils, with prominent involvement of autoimmune reactions, caused by IgG antibodies, either specific to FcεRI or IgE, resulting in release of mediators of inflammation, e.g., histamine (3).

Treatment options currently include use of second generation H1 antihistamines in first line, often increasing dosages up to four times of standard doses if required (4). However, increase of dosages of antihistamines does not provide sufficient control over symptoms in a proportion of patients (2). Second-line biological drugs like omalizumab are used for treatment of refractory forms of CSU; however, there are still many cases that cannot be fully treated using current approaches (3).

Bruton's tyrosine kinase is a critical signaling protein involved in regulation of signaling in B-cells, as well as activation of mast cells and basophils through FcεRI. Therefore, blocking BTK offers a promising way to inhibit degranulation of mast cells, as well as autoantibody-dependent pathways, associated with CSU (3,5). In addition, this therapy may address underlying pathophysiological mechanisms in CSU effectively (5). This narrative review aims to summarize current information regarding mechanisms of action, efficacy, safety, and prospects of Bruton's tyrosine kinase inhibitors in treatment of chronic spontaneous urticaria.

2. Methods

This review set out to incorporate the current literature on the use of Bruton tyrosine kinase (BTK) inhibitors in chronic spontaneous urticaria (CSU). The search in the literature was performed through PubMed, Embase, and ClinicalTrials.gov sources to find the relevant publications starting with the beginning of each of the databases until February 2026. The queries were made using a combination of the following; Bruton’s tyrosine kinase, BTK inhibitor, chronic spontaneous urticaria, CSU, mast cells, basophils and the names of the investigative drugs; remibrutinib and rilzabrutinib.

The additional eligible studies were searched manually using the bibliographies of the selected articles and the review articles on the subject matter.

Articles were chosen based on the criteria of them studying the application of BTK inhibitors in CSU, thematic studies on the pathophysiologic processes involved in BTK signaling and mast cell/basophil activation, or emerging therapeutic strategies in BTK urticaria. They included randomized controlled trials, phase I-III clinical trials, observational studies and review articles. The studies included in preclinical studies should have brought any insight into the pathophysiologic mechanisms that underline the disease.

Since it is a narrative review, there was neither a risk-of-bias evaluation nor meta-analysis. Instead, the findings were combined in a descriptive manner, with therapies, safety, pathophysiology, and new research trends on BTK-targeted therapy in CSU being identified.

3. Bruton’s Tyrosine Kinase: A Pivotal Player in Urticaria Pathogenisi

Bruton’s tyrosine kinase (BTK) is a Tec family non-receptor tyrosine kinase encoded by the X-linked BTK gene and is essential for B-cell maturation as well as innate immune signaling in mast cells and basophils—the principal effector cells in chronic spontaneous urticaria (CSU) (6,7). Accumulating evidence implicates BTK as a central signaling hub in both major CSU endotypes: the autoallergic (type I) form, mediated by IgE autoantibodies against self-antigens, and the autoimmune (type IIb) form, driven by IgG autoantibodies targeting FcεRI or IgE (6,8).

Engagement and aggregation of the high-affinity IgE receptor (FcεRI) result in recruitment of BTK to the plasma membrane via its pleckstrin homology domain binding to phosphatidylinositol-3,4,5-trisphosphate. Subsequent phosphorylation of BTK—particularly at the activation loop residue Y551 by Src family kinases such as Lyn—enables activation of downstream effectors, including phospholipase C-γ2 (PLCγ2) (6,9). Activated PLCγ2 hydrolyzes phosphatidylinositol-4,5-bisphosphate into inositol-1,4,5-trisphosphate and diacylglycerol, triggering intracellular calcium mobilization and activation of protein kinase C, NF-κB, and mitogen-activated protein kinase pathways. These signaling events ultimately lead to mast cell degranulation, resulting in the release of histamine and tryptase. They also promote the generation of lipid mediators, including leukotriene C4 and prostaglandin D2, along with the production of pro-inflammatory cytokines such as interleukin (IL)-4, IL-5, IL-13, and tumor necrosis factor-α. Together, these mediators drive both the immediate wheal-and-flare response and the subsequent late-phase inflammatory reaction (6,8,10).

In addition to its role in mast cell activation, BTK contributes to CSU pathogenesis by supporting the survival and functional activity of autoreactive B cells through B-cell receptor signaling. This process enhances the generation of pathogenic autoantibodies (7,11). Experimental models lacking functional BTK demonstrate markedly impaired FcεRI-mediated signaling, reduced histamine release, and protection from anaphylactic responses (6,9). Consistent with these findings, increased expression of phosphorylated BTK has been observed in lesional skin of patients with CSU, supporting its pathogenic relevance in human disease (6).

The clinical relevance of BTK signaling in CSU is underscored by recent phase 2 and phase 3 trials of oral BTK inhibitors. In the REMIX-1 and REMIX-2 studies, remibrutinib (50 mg twice daily) produced rapid and sustained improvements in disease activity, with mean reductions in weekly Urticaria Activity Score (UAS7) of approximately 45–68% from baseline compared with placebo, and onset of efficacy observed as early as week 1 (12,13,15). Rilzabrutinib (400 mg once daily) demonstrated comparable efficacy, achieving approximately 45% mean UAS7 reduction in phase 2 evaluation(14).These agents were generally well tolerated over treatment periods extending up to 52 weeks, with predominantly mild-to-moderate infections reported as the most common adverse events (12–15).

Unlike omalizumab, which neutralizes circulating IgE, BTK inhibition suppresses intracellular signaling downstream of both IgE- and IgG-mediated mast cell activation, thereby targeting multiple pathogenic pathways implicated in CSU (7,11). This proximal blockade of effector cell activation positions BTK inhibitors as promising oral precision therapies for patients with antihistamine-refractory or biologic-resistant CSU.

4. Bruton's Tyrosine Kinase Inhibitors: A New Therapeutic Class for CSU

4.1. Overview of Availabe and Investigational BTK Inhibitors

Among targeted therapies, Bruton's tyrosine kinase (BTK) inhibitors are a class that modulate signaling pathways within immune cells involved in their activation. BTK participates in signaling after activation of the high-affinity IgE receptor (FcεRI) within mast cells and basophils, and also in B-cell receptor signaling. This makes it a root driver of chronic spontaneous urticaria. The ability of BTK inhibitors developed for oncology in early clinical studies to suppress IgE-mediated cellular activation supported its emergence as a therapeutic target for allergic and autoimmune diseases (6).

Based on their binding characteristics and mode of interaction, BTK inhibitors can be divided into distinct categories. One group consists of covalent irreversible inhibitors, which achieve prolonged kinase inhibition by forming a permanent bond with the Cys481 residue in the ATP-binding pocket (6,9). This class includes early-generation agents like acalabrutinib and ibrutinib, along with more selective compounds developed for non-cancerous conditions. Some examples include tirabrutinib, TAS5315, evobrutinib, and tolebrutinib (6,9,16,18). Non-covalent inhibitors bind differently; they interact temporarily with BTK, thereby allowing reversal of the inhibition, and thus drug dissociation (6,9,18). In addition to this, a recent subcategory of more novel agents has emerged. An example of this is rilzabrutinib, which merges covalent binding with reversibility. This is intended to attain sustained target binding while limiting unintended reactions (6,9,14).

Of the BTK inhibitors studied in chronic spontaneous urticaria, remibrutinib is currently the most advanced agent in development. It is a covalent irreversible inhibitor. It is orally delivered and highly specific. It has advanced into final-stage trials, which include CSU cohorts who remain symptomatic despite treatment with H1-antihistamines(6,16,17). Rilzabrutinib is another agent that remains under ongoing research. It is a covalent yet reversible BTK inhibitor that has passed intermediate clinical trials for CSU, awaiting further development (14). Furthermore, TAS5315 is a covalent BTK inhibitor that has been analyzed in initial research phases for CSU, which is refractory to antihistamines, which validates further research into this disease (16).

There are a variety of BTK inhibitors currently in research and development. One drug, in particular, is fenebrutinib, which is a non-covalent reversible antagonist. It has undergone Phase II trials for CSU but has been discontinued for this disease. However, it continues to be developed for alternative immune-mediated diseases (6,14,17) . Consequently, biochemical and clinical assessment of BTK blockers for CSU remains active (6,17). Early-stage trials show

that sofnobrutinib reduced B-cell and basophil activation, which validates a clear rationale for future investigation (18). Collectively, these molecules demonstrate the diversity in kinase blocker frameworks and clinical phases currently being explored, which validates the ongoing research into BTK inhibition for CSU (6,17).

4.2. Pharmacological Profiles of BTK Inhibitors

Identifying BTK as a therapeutic target for CSU is important as this link connects extracellular receptors with triggering of mast cells. The subsequent phosphorylation reactions inside mast cells and basophils occurs when IgG autoantibodies or IgE-autoallergen complexes support cross-linking of FcεRI. Throughout this cascade, the transmission of impulses to downstream effector proteins is driven by the cellular degranulation and the release of inflammatory mediators. When BTK inhibitors interrupt this sequence at a specific step, there is a reduction of acute and late-phase mast cell reactions associated with CSU (6).

Resistance profiles, along with duration of inhibition and selectivity, are dictated by how BTK blockers are pharmacologically classified based on their reversibility and binding nature. Restoration of enzymatic function remains inactive until new BTK protein is produced because the covalent irreversible agents form a permanent bond with the stable Cys481 residue inside the ATP-binding site of BTK. As a result, pharmacodynamic effects may persist even after systemic drug levels decline (6,9). Remibrutinib follows this pattern through covalent Cys481 binding with preferential interaction with the inactive form of BTK. Target inhibition persists despite a short circulating half-life (6,9,17).

Table 1: Classification and pharmacological profiles of Bruton's tyrosine kinase (BTK) inhibitors. This table summarizes the binding characteristics, reversibility, and target selectivity of both first-generation and next-generation BTK inhibitors. It highlights the pharmacological evolution from broad-spectrum, irreversible agents (e.g., ibrutinib) to the highly selective, covalent and non-covalent inhibitors currently in clinical development for chronic spontaneous urticaria (CSU).

Drug	Binding Type	Reversibility	Target Selectivity	Clinical Development Phase for CSU	References
Remibrutinib	Covalent (binds inactive BTK conformation at C481; covalent bond confirmed by LC/MS and crystal structure)	Irreversible	Highly selective; off-target activity only against BMX and TEC; negligible activity against GPCRs and nuclear receptors	Phase III completed (REMIX-1 & REMIX-2); NDA under review	(Ref. 33,34)
Rilzabrutinib	Non-covalent	Reversible	Highly selective; suppresses FcεRI-mediated mast cell degranulation without significantly impairing B-cell development	Phase II completed (RILECSU); Phase III planning ongoing	(Ref. 14)
Fenebrutinib	Non-covalent	Reversible; rapid loss of cellular BTK inhibition after washout confirmed	Highly selective; 130× more selective for BTK vs. other kinases; Ki = 0.91 nM	Phase II completed in CSU; no further CSU trials planned; currently in Phase III for MS	(Ref.17,34)
Ibrutinib	Covalent (binds C481 of BTK active conformation)	Irreversible	Broad/low selectivity; active against TEC kinase, EGFR, ITK, and several other kinases	Not specifically developed for CSU; FDA-approved for B-cell malignancies; occasional off-label use	(Ref. 6, 35)

Conversely, non-covalent reversible inhibitors such as fenebrutinib interact transiently with BTK. Their pharmacodynamic effects depend on sustained plasma exposure. Sustained serum bioavailability remains crucial for non-covalent reversible blockers like fenebrutinib, as these agents engage BTK only transiently (6,17). The hybrid character of rilzabrutinib is that of a reversible covalent bond. This ensures that receptor saturation remains extended while still enabling dissociation to occur as protein turnover unfolds (6,14).
The clinical justification for BTK blockade in CSU is governed by pharmacodynamic and pharmacokinetic effects. For instance, remibrutinib undergoes quick absorption after oral intake and displays rapid clearance with minimal buildup. Nevertheless, it maintains a prolonged BTK binding due to its permanent linkage (6,9). Biological activity appears to be a function of target occupancy rather than circulating drug concentration (9). Selectivity for BTK relative to the TEC kinase family is critical. Early-generation covalent inhibitors were associated with off-target interactions involving inhibition of related kinases (6). Newer agents have been developed to improve BTK selectivity by using conformational binding preferences. This reduces unintended kinase inhibition while maintaining suppression of FcεRI signaling (6,9). These features form a framework supporting the continued development of both covalent and non-covalent BTK inhibitors as targeted therapies for CSU (Table 1) (6,17).

5. Clinical Efficacy of BTK Inhibitors in Chronic Spontaneous Urticaria

5.1. Efficacy in Antihistamine-Refractory Chronic Spontaneous Urticaria

High weekly Urticaria Activity Score values reflecting moderate to severe disease at baseline are presented by specific patients where the clinical efficacy of Bruton tyrosine kinase (BTK) inhibitors has been intensely studied. These patients were refractory to treatment by second-generation H1 antihistamines. Routine patient care was upheld during the study period because patients continued their background antihistamine regimens throughout both Phase 2 and Phase 3 clinical trials. The change in the weekly Urticaria Activity Score compared to baseline acted as the primary efficacy measure throughout these investigations. Secondary metrics comprised hive and itch severity along with angioedema activity. Evaluation also focused on critical responder outcomes, such as complete response and well-controlled disease, denoted by UAS7 values of 0 and 6 or less, respectively (14,15,19) .

Early clinical evidence was provided by phase 2 randomized, double-blind, placebo-controlled trials evaluating oral BTK inhibition in antihistamine-refractory CSU (14,19). In the RILECSU phase 2 trial, rilzabrutinib showed significant reductions in both UAS7 and ISS7 at week 12 compared with placebo at the highest tested dose, with symptomatic improvement observed within the first week of treatment (14) . Similar outcomes were reported in a phase 2b dose-finding study of remibrutinib, in which reductions in UAS7 were observed across all evaluated doses relative to placebo, with rapid symptom improvement observed from week 1 and maintained throughout the 12-week double-blind phase (19).

Definitive confirmation of these findings was provided by the phase 3 REMIX-1 and REMIX-2 trials, where remibrutinib 20 mg twice daily achieved significantly greater reductions in UAS7 at week 12 than placebo, alongside higher proportions of patients attaining well-controlled disease and complete response. The magnitude of response reported in phase 3 studies surpassed the predefined minimal clinically important difference for UAS7, highlighting the clinical importance of BTK inhibition in this group of patients. (15)
Long term outcomes from the 52- week extension phase of the REMIX study further demonstrated durable results, with consistent reductions in UAS7, ISS7 and HSS7, maintained throughout the year with continuous therapy, including patients who transitioned from placebo to active therapy at week 24. (5)
Across the Phase 2 and 3 trials, evidence suggests that BTK-inhibition therapy leads to a prompt and sustained clinically significant symptom control among CSU patients who are refractory to treatment with H1-antihistamines (Table 2) (14,15,19,5).

5.2. Efficacy in Omalizumab-Refractory Chronic Spontaneous Urticaria

Subgroup analyses conducted in phase 2 and phase 3 trials involving participants with prior exposure to anti-IgE agents demonstrated the efficacy of BTK-targeted inhibitors in omalizumab-refractory chronic spontaneous urticaria. Improvements in weekly UAS7 scores were noted in both the phase IIb remibrutinib study and the RILECSU rilzabrutinib trial, regardless of prior treatment with omalizumab, indicating preserved clinical efficacy in biologic-exposed CSU patients. The phase III REMIX-1 and REMIX-2 trials also supported these findings, with about one-third of enrolled participants having prior exposure to omalizumab. Subgroup analyses demonstrated sustained therapeutic effectiveness of remibrutinib compared with placebo throughout 52 weeks of follow-up (15,5).These findings indicate that BTK inhibition continues to show clinical efficacy in CSU patients despite prior treatment with omalizumab (14,15,19,5).

5.3. Comparative Efficacy

The absence of direct comparative clinical trials currently limits the proper evaluation of BTK inhibitors in CSU. As a result, current evidence is drawn from indirect comparisons across individual placebo-controlled trials. Reductions in UAS7 and overall symptom control indicating clinical efficacy of BTK-targeted therapy were consistently reported across these trials (Figure 1). Comparison of response rates across

Table 2: Key clinical efficacy trials evaluating BTK inhibitors in antihistamine-refractory chronic spontaneous urticaria. This table consolidates primary endpoints and key clinical outcomes from recent phase II and phase III trials, including REMIX-1, REMIX-2, and RILECSU. The extracted data demonstrate rapid, clinically meaningful, and sustained reductions in the Urticaria Activity Score (UAS7) compared to placebo across patient populations.

Trial Name/Phase	Drug & Dosage	Patient Population	Primary Endpoint	Key Clinical Outcomes	References
REMIX-1 (Phase III)	Remibrutinib 25 mg BID oral	Adults with moderate-to-severe CSU symptomatic despite second-generation H1-antihistamines; prior anti-IgE biologic use not exclusionary	Change from baseline in UAS7 at week 12	LS mean UAS7 change: −20.0 ± 0.7 (remibrutinib) vs. −13.8 ± 1.0 (placebo), P<0.001; UAS7 ≤6 achieved in 49.8% vs. 24.8% at week 12; improvement seen as early as Week 1; sustained through Week 52	(Ref. 15)
REMIX-2 (Phase III)	Remibrutinib 25 mg BID oral	Identical design to REMIX-1: adults with moderate-to-severe CSU refractory to H1-AH; randomized 2:1 over 24 weeks	Change from baseline in UAS7 at week 12	LS mean UAS7 change: −19.4 ± 0.7 vs. −11.7 ± 0.9, P<0.001; UAS7 ≤6 in 46.8% vs. placebo; by Week 52, 35.1% reached UAS7=0 (complete response)	(Ref. 15)
RILECSU (Phase II)	Rilzabrutinib 400, 800, 1200 mg/d vs. placebo	Adults with moderate-to-severe CSU refractory to H1-antihistamines; 52-week study (12-week DBPC + 40-week OLE)	Change from baseline at week 12 in ISS7 (US) or UAS7 (non-US)	At 1200 mg/d dose: ISS7 LS mean change −9.21 vs. −5.77 (P=0.02); UAS7 LS mean change −16.89 vs. −10.14 (P=0.02); early improvements at Week 1; biomarkers (IgG anti-FcεRI, IL-31) reduced	(Ref. 14)
Fenebrutinib (Phase II)	Fenebrutinib 200 mg BID oral	Adults with moderate-to-severe CSU refractory to up to 4× approved H1-AH dose	Change from baseline in UAS7 at week 8	Near-maximal efficacy observed at Week 4; clinically meaningful treatment benefit demonstrated in antihistamine-refractory patients; no further CSU trials planned	(Ref. 11,17)

studies is limited by variability in study design, patient populations, baseline severity of disease, prior therapeutic exposure, and treatment regimens. Consequently, definitive assessment of comparative efficacy will require direct head-to-head trials and real-world data (14,15,19,5).

vary considerably depending on drug specificity and individual patient factors (21).

The first generation of BTK inhibitors, which is represented by ibrutinib, has been through the most extensive investigation (22). Frequently reported adverse events from the combined randomised clinical trials include diarrhoea, fatigue, nausea and

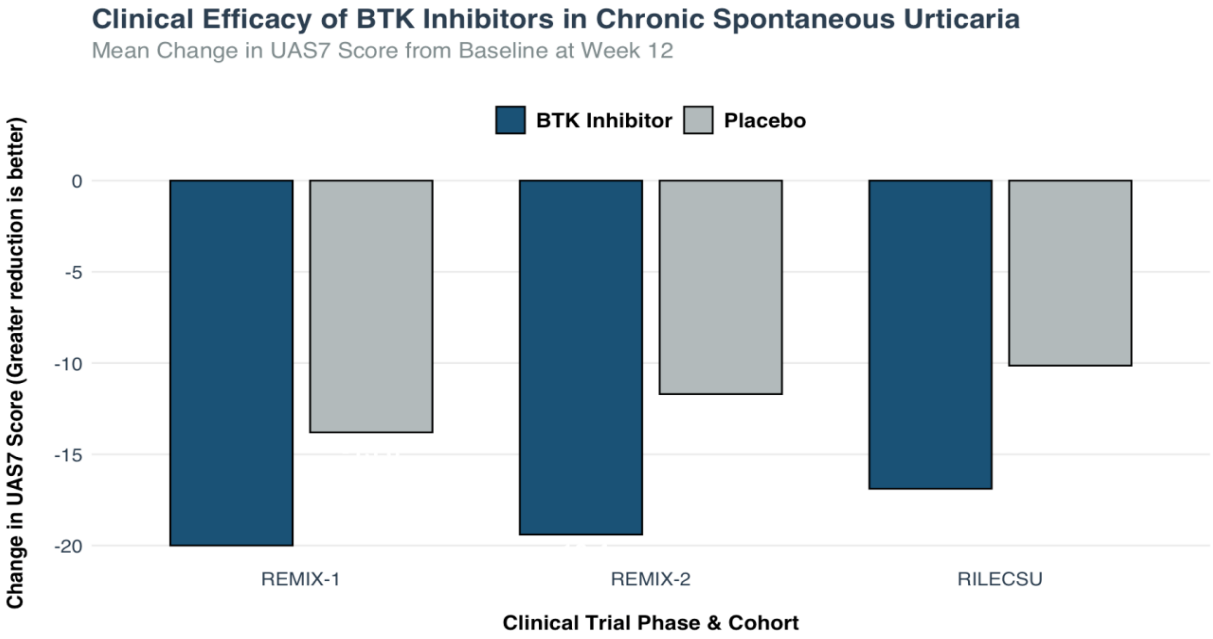

Figure 1: Clinical efficacy of targeted BTK inhibition in antihistamine-refractory CSU. The grouped bar chart illustrates the mean reduction in the Urticaria Activity Score over 7 days (UAS7) from baseline to week 12 across key clinical trials. Data reflect outcomes from the phase III REMIX-1 and REMIX-2 trials evaluating remibrutinib (25 mg twice daily), and the phase II RILECSU trial evaluating rilzabrutinib (1200 mg daily) compared with placebo. Greater negative values denote superior symptom reduction and disease control.

6. Safety and Tolerability Profile of Bruton Tyrosine Kinase Inhibitors

Bruton tyrosine kinase (BTK) inhibitors have become an important component in the therapeutic armamentarium for the treatment of various B-cell malignancies, including chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenström macroglobulinemia (20). Although these agents demonstrate significant clinical efficacy, a thorough evaluation of their safety and tolerability profiles is essential, particularly given the prolonged duration of treatment in a substantial proportion of patients. In general, BTK inhibitors are considered manageable in terms of adverse effects; however, their toxicity profiles

musculoskeletal discomfort. These sequelae are usually mild to moderate and show up early in the therapeutic process. Diarrhoea is fairly self limiting and a break in dosage is rarely required (23). Although fatigue is common, it is usually amenable to supportive measures and rarely is the cause for discontinuation of therapy.

Nevertheless, ibrutinib is associated with several toxicities which are clinically important. Among them, the importance of cardiovascular adverse events with atrial fibrillation and hypertension being the leading concerns is the first in order of seriousness. Atrial fibrillation is more common with age and in subjects with pre-existing heart pathology (23). Even though most of the cases are treatable using medical therapy, some patients require a dose cut or total withdrawal. Hypertension, as a result of long-term exposure to ibrutinib, should be one of the topics of interpretation by

regularly checking the blood pressure and the use of corresponding treatment (24).

The bleeding complications are one more safety issue. Bruton tyrosine kinase is part of platelet signal transduction, and pharmacologic inhibition of which has been reported to increase the hemorrhagic risk (25). Although most bleeding episodes are milder ones in nature (in the form of bruising or epistaxis), severe hemorrhage has also been reported, especially in patients who are taking anticoagulants or antiplatelet therapy at the same time. Therefore, careful assessment of bleeding risk has been recommended before the start of the therapy process.

Another type of adverse events with BTK inhibitors consists in infections. Infections of the upper respiratory tract are noted to be frequent, and much more severe infections, like pneumonia, are relatively rare. Opportunistic infections are rare, but have been reported otherwise, particularly in the heavily pretreated patient. Immunological disturbance due to the disease and exposure to the previous therapy both modulate the risk of infection and makes it difficult to establish a direct causal relationship with BTK inhibition alone (26).

BTK inhibitors concepts (Acalabrutinib and zanubrutinib) have been designed so that they display a stronger selectivity in BTK and therefore reduce the effects of off-target. These new agents have a relatively positive safety profile, according to clinical trials, as compared to ibrutinib; the incidence rates of atrial fibrillation and hypertension tend to decrease, and adverse events forcing the discontinuation of therapy are less frequent (Figure 2) (27).

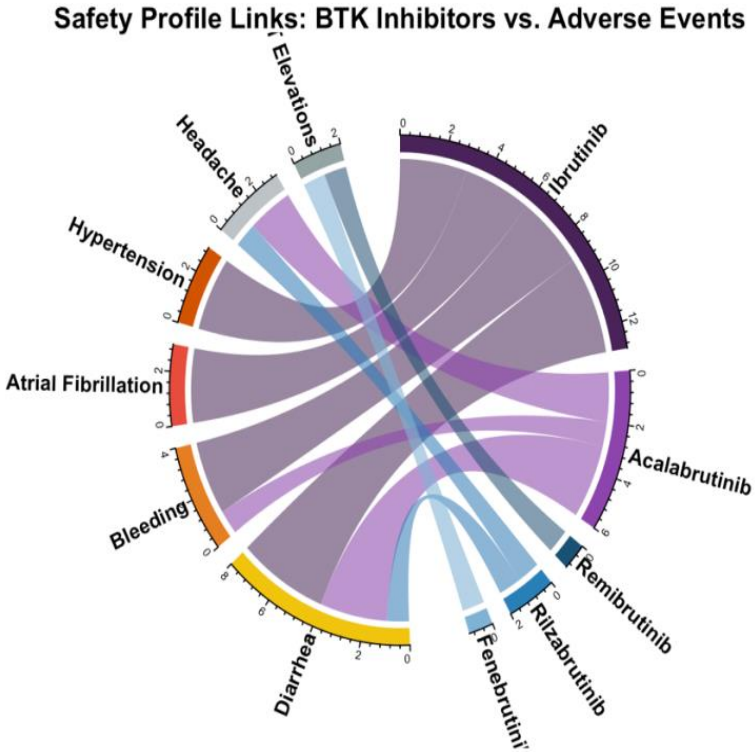

Figure 2: Chord diagram mapping the safety profiles and adverse event burdens across generations of BTK inhibitors. The width of the connecting bands represents the relative clinical frequency and severity of specific adverse events associated with each pharmacological agent. First-generation, covalently binding inhibitors with broader kinase activity (e.g., ibrutinib) demonstrate strong associations with severe, therapy-limiting cardiovascular and hemorrhagic events, including atrial fibrillation and bleeding. Conversely, next-generation, highly selective agents currently in development for CSU (e.g., remibrutinib, rilzabrutinib, fenebrutinib) exhibit minimal off-target toxicity, connecting primarily to mild, manageable events such as headache, diarrhea, or transient transaminase elevations.

Table 3: Comparative safety and tolerability profiles across generations of BTK inhibitors. This table contrasts the common and severe adverse events associated with early-generation oncology agents versus newer, highly selective inhibitors. Next-generation agents developed for CSU (e.g., remibrutinib, rilzabrutinib) demonstrate highly favorable safety profiles with minimal cardiovascular or hemorrhagic risks, significantly reducing therapy-limiting toxicities.

Agent / Generation	Most Common Adverse Events	Severe/Rare Adverse Events	Notes on Discontinuation	References
Ibrutinib (1st gen, covalent, broad-spectrum)	Diarrhea, upper respiratory tract infection (URTI), fatigue, bleeding, skin rash	Atrial fibrillation (6–16%); hypertension (23.2%); ventricular arrhythmias; all-grade bleeding 51.3%; neutropenia; hepatitis B reactivation	Discontinuation due to AEs is substantial; cardiovascular AEs are therapy-limiting, especially cumulative AF and bleeding	(Ref. 6,35,37,38)
Acalabrutinib (2nd gen, covalent, more selective)	Diarrhea (53%), headache (42%), contusion (40%), dizziness (33%), URTI (33%), cough (30%)	AF 9.4%; hypertension 9.4%; all-grade bleeding 38%; eosinophilia (grade 1–2); hep B reactivation risk	Discontinuation due to AEs: ~17% in CLL trials; major hemorrhage in ~1%; better tolerated than ibrutinib	(Ref. 6,39)
Remibrutinib (Next-gen, covalent highly selective)	Generally mild; mild transaminase elevation in some patients; cytopenias mild/not associated with infections	No significant cardiovascular signals; cytopenias mild and non-infectious; safety profile favorable	Low discontinuation rate; favorable safety profile confirmed through Week 52 in REMIX-1/-2	(Ref. 6,39)
Rilzabrutinib (Next-gen, non-covalent reversible)	Diarrhea, nausea, headache (occurring at higher frequency vs. placebo)	No events of cytopenia, bleeding, or atrial fibrillation observed in RILECSU trial	Favorable risk-benefit profile; well tolerated across all dose groups in Phase II	(Ref. 14)
Fenebrutinib (Next-gen, non-covalent reversible)	Generally, well tolerated at 200 mg BID in CSU trial; mild LFT elevation possible	No major cardiovascular events in Phase II CSU trial	No data on long-term discontinuation for CSU; ongoing MS trials may inform future safety	(Ref. 17)

The most common side effect linked to acalabrutinib is headache, which commonly occurs at the beginning of the treatment cycle and is effectively treated with over-the-counter drugs or caffeine. Gastrointestinal disorders and fatigue are not left out either and they are generally mild (28). However, compared with zanubrutinib, cardiotoxicity and hemorrhagic events were less common; however, neutropenia tends to be more common. Notably, these hematologic defects are in most cases without symptoms and can be controlled efficiently in terms of dose or supportive treatment. (Table 3)

7. Integrating BTK Inhibitors into the CSU Treatment Algorithm and Future Perspectives

7.1. Proposed Placement in The Treatment Algorithm

The management of CSU today adopts a step-up approach, where second-generation H1-antihistamines are first used, followed by dose up-titration, and eventually biologic therapy, predominantly omalizumab is used in cases where the disease is antihistamine-refractory (Figure 3) (29). While this algorithm has significantly benefited the disease control of a large number of patients, it is still constrained by the delayed response time, partial response rates, and the presence of the refractory disease in a clinically significant proportion of patients. The BTK inhibitors provide a mechanistically different therapeutics approach, which directly interferes with intracellular signaling pathways that are core to the mast cell and basophil activation. BTK inhibitors, in contrast to omalizumab, disrupt the downstream transmission of FceRI- and Fcg receptor-mediated signaling, and thus prevent the release of mediators, independent of the presence of upstream IgE (30).

One of the most significant benefits of BTK inhibitors is that, unlike injectable biologics, it is orally delivered, and it can be beneficial in patient acceptability and adherence and flexibility in disease management in the long term. Furthermore, preliminary clinical trial results show that BTK inhibitors are highly likely to induce rather rapid symptom improvement, and therefore BTK inhibitors can be used as an inductive therapy of patients with a severe disease activity or as a bridging agent in the treatment of patients with refractory CSU (6). The optimal application of BTK inhibitors as an alternative or even as an addition to biologic therapy will be established in the future where comparative efficacy data, the safety outcomes in the long-term, and real-life performance will be provided.

The combination strategies can also be developed particularly in patients who respond partially to the existing treatments. These approaches should however be considered with caution on the cumulative

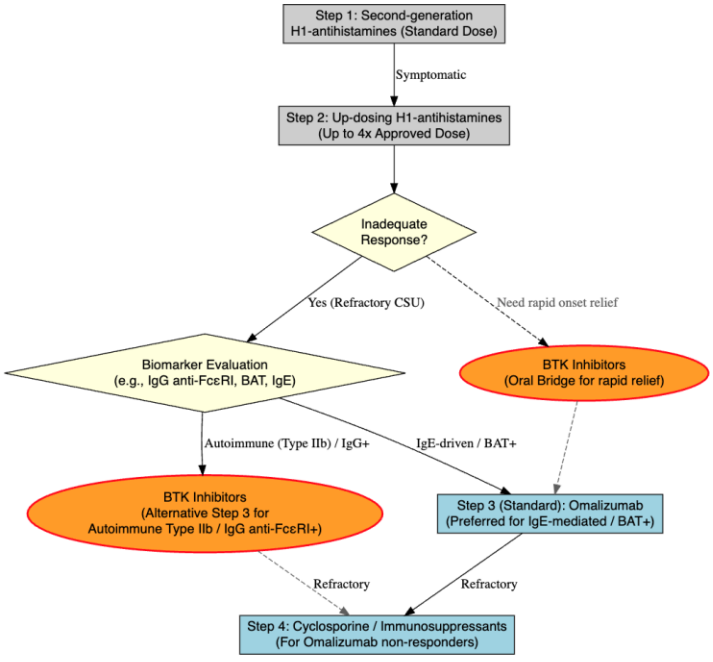

Figure 3: Proposed integration of Bruton's tyrosine kinase (BTK) inhibitors into the step-up treatment algorithm for chronic spontaneous urticaria (CSU). The algorithm builds upon current EAACI/GA²LEN management guidelines. Following the failure of standard and up-dosed second-generation H1-antihistamines, BTK inhibitors are proposed as either a rapid-onset oral bridge prior to biologic therapy, or as an alternative third-line option for patients who are refractory to or ineligible for omalizumab. Decision nodes highlight the potential role of biomarker evaluation such as the presence of IgG anti-FcεRI antibodies or basophil activation test (BAT) results in guiding targeted patient stratification.

immunomodulatory effects, safety and the pharmacoeconomic impact. With the change in evidence, the BTK inhibitors are expected to induce a redefinition of existing CSU treatment algorithms into a more mechanism-oriented framework.

7.2. Patient Selection and Biomarkers for Response

The heterogeneous nature of CSU underscores the importance of identifying the patients with the highest chances of responding to specific treatment. There is growing evidence to confirm the presence of specific disease endotypes especially autoimmune CSU, which is autoantibodies against IgE or FcεRI and a severe disease, less responsive to antihistamines and omalizumab (16). Considering the key role of BTK in B-cell receptor signal transmission and induction of Fc receptor mediated effector cells, autoimmune patients can be considered a biologically plausible target group in BTK inhibition.

The clinical features that could be associated with a favourable response are severe baseline disease activity, the presence of angioedema, the comorbidity of autoimmune diseases, and histories of biologic failure. Markers that can be further used in patient selection include laboratory-based markers, including a positive autologous serum skin test, anti- FcεRI or anti-IgE autoantibodies, altered basophil counts, or abnormal basophil activation tests (31). These markers are immune pathways that BTK directly regulates and thus could be of specific importance to treatment stratification.

In addition to traditional biomarkers, transcriptomic and proteomic profiling of lesional skin and peripheral blood provides an option to discover the molecular signature of BTK pathway activation. The initial work on exploratory studies indicates that changes in mast cell-generated cytokines and other inflammatory mediators are associated with changes in response to BTK inhibition and indicate the possibility of precision medicine to CSU (32). Nevertheless, the absence of validated and standardized biomarkers is still a significant drawback and clinical trials in the future ought to incorporate biomarker discovery and validation as a primary goal, and not a secondary analysis.

7.3. Unanswered Questions and Future Research Directions

Although promising initial results have been noted, there are still a number of gaps in knowledge that need to be addressed. The most important of them is the issue of long-term disease control and modification (7,31). Although BTK inhibitors are observed to be effective in suppressing symptoms, the long-term inhibition of the pathways remains unclear to cause long-term remission or change the natural course of CSU in response to treatment withdrawal (5,31).

The effectiveness of BTK inhibitors in various CSU endotypes is also worth systematic consideration (6,8). Direct comparisons between BTK inhibitors and omalizumab and new biologic in trials are needed to determine their effectiveness relative to each other in terms of response speed, degree of benefit, and safety (11). Furthermore, the data of special populations, such as pediatric patients, pregnant people, and individuals with serious comorbidities, is also missing to make the existing data generalizable (7,27).

Real-world evidence will be important in explaining treatment adherence and patient-reported outcomes, which usually vary in real world examples as compared to the controlled trial environments (18). The other factor that must be addressed is cost-effectiveness and availability particularly in health care systems that have limited resources, oral small molecule therapy may be advantageous as compared to high-cost biologics (7).

Finally, highly selective next-generation BTK inhibitors that are less accompanied by side effects can be created to further expand the therapeutic exposure to chronic dosing (20). Collectively, these developments place BTK inhibition not simply as an additional treatment option, but as a potential paradigm shift to intracellular, mechanism-based management of CSU (6,31).

8. Conclusion

The inhibition of the selective Bruton tyrosine kinase (BTK) is a conceptually sound and promising treatment strategy in patients with chronic spontaneous urticaria (CSU). There is developing trial evidence which suggests that remibrutinib and rilzabrutinib drugs lead to rapid, meaningful, and acceptable short-term safety profiles in patients who are antihistamine-refractory. The findings are in line with the preclinical experiments that IgE- and autoantibody-mediated models show that BTK inhibition suppresses the IgE- and autoantibody-mediated mast cell and basophil activation.

Nevertheless, there are still some major uncertainties: the safety and durability of response in the long term, its

relative efficacy in comparison with existing biologic therapy (e.g., Omalizumab), biomarkers to use when selecting patients, and the real-world effectiveness and cost-effectiveness. The priority areas of future research are the completion of phase III trials underway, direct-comparison studies, long-term extensions studies, and safety registry studies, and research on access and affordability, especially in resource-limited environments.

Herein, we summarized the existing evidence and outlined the translational and clinical questions, which must be resolved before BTK inhibitors can become a widely used treatment message in CSU therapy. Through intensive testing in the long-term and equal access, BTK inhibition can offer more and better treatment opportunities to patients with refractory CSU.

Conflict of interest The authors declare no conflict of interest in this study. No financial or personal relationships with other individuals or organizations that could influence this research were observed.

Acknowledgments The authors would like to express their sincere gratitude to Dr. Shahid Ullah Khan, Assistant Professor of Biochemistry at Dubai Medical University, for his guidance and insightful feedback throughout this process. We also thank Dubai Medical University (DMU) for providing a supportive academic environment and resources that facilitated this study.

Funding The authors have not received any funding to conduct the research.

AI Declaration Artificial intelligence tools (ChatGPT OpenAI) were not used in the preparation of this manuscript, except for minor assistance in reviewing and correcting citation formatting, including reference numbering, naming consistency, and punctuation. The authors reviewed and verified all content and take full responsibility for the accuracy, originality, and integrity of the work.

Author Contributions

1. **Zainab Abdul Hamid (Corresponding Author)** – Dubai Medical University, Dubai, United Arab Emirates.
   o Conceptualization, project administration, writing – original draft, and writing – review & editing.
2. **Afsheen Azhar** – Dubai Medical University, Dubai, United Arab Emirates.
   o Contribution to conceptualization, writing – original draft, and writing – review & editing.
3. **Naveed Ahmad** – Khyber Medical College, Peshawar, Pakistan.
   o Participation in methodology development, writing – original draft, and manuscript review & editing.
4. **Rahat Ullah** – Gomal Medical College, Dera Ismail Khan, Pakistan.
   o Contribution to writing – original draft and manuscript preparation.
5. **Umaima** – Dubai Medical University, Dubai, United Arab Emirates.
   o Involvement in validation, formatting, and reference checking.
6. **Muhammad Yousaf** – Gomal Medical College, Dera Ismail Khan, Pakistan.
   o Contribution to writing – original draft and manuscript preparation.
7. **Bahar Ullah** – Saidu Medical College, Swat, Pakistan.
   o Participation in writing – original draft and manuscript preparation.
8. **Safi Ullah Khan** – Bahria University Medical and Dental College, Karachi, Pakistan.
   o Contribution to writing – original draft and manuscript preparation.
9. **Nighat Aziz** – Gomal Medical College, Dera Ismail Khan, Pakistan.
   o Supervision, formal analysis, and visualization.

References

1. Saini SS. Chronic spontaneous urticaria: etiology and pathogenesis. Immunology and Allergy Clinics of North America [Internet]. 2014 Feb 1 [cited 2021 Jul 25];34(1):33–52. Available from: https://pubmed.ncbi.nlm.nih.gov/24262688/
2. Tbakhi B, Ware K, Park HS, Bernstein JS, Bernstein JA. An Overview of Chronic Spontaneous Urticaria: Diagnosis, Management, and Treatment. Allergy, Asthma & Immunology Research. 2025;17(5):531
3. Criado PR, Criado RFJ, Miot HA, Abdalla BMZ, Marchioro HZ, Bonamigo RR. Chronic spontaneous urticaria: update on pathogenesis and therapeutic implications. Anais Brasileiros de Dermatologia [Internet]. 2025 Sep [cited 2025 Sep 27];100(5):501198. Available from: https://www.anaisdedermatologia.org.br/en-chronic-spontaneous-urticaria-update-on-articulo-S0365059625001400

4. Kaplan AP. Chronic Spontaneous Urticaria: Pathogenesis and Treatment Considerations. Allergy, Asthma & Immunology Research. 2017;9(6):477.
5. Giménez-Arnau AM, Szalewski R, Hide M, Jain V, Abdallah Khemis, Lebwohl M, et al. Remibrutinib in chronic spontaneous urticaria: 52-Week results from two phase 3 studies. Journal of Allergy and Clinical Immunology. 2025 Oct 1;
6. Bernstein JA, Maurer M, Saini SS. BTK signaling—a crucial link in the pathophysiology of chronic spontaneous urticaria. Journal of Allergy and Clinical Immunology. 2023 Dec 1.
7. Lauletta G, Potestio L, Patruno C, Cantelli M, Napolitano M. The emerging role of Bruton's tyrosine kinase inhibition in urticaria management. Expert Opinion on Drug Safety. 2025 Jan 29;24(5):507–12
8. Kaplan A, Lebwohl M, Giménez-Arnau AM, Hide M, Armstrong AW, Maurer M. Chronic spontaneous urticaria: Focus on pathophysiology to unlock treatment advances. Allergy. 2022 Dec 7;
9. Mendes-Bastos P, Brasileiro A, Kolkhir P, Frischbutter S, Scheffel J, Moñino-Romero S, et al. Bruton's tyrosine kinase inhibition—An emerging therapeutic strategy in immune-mediated dermatological conditions. Allergy. 2022 Feb 28;77(8):2355–66.
10. Ilaria Puxeddu, Pistone F, Pisani F, Levi-Schaffer F. Mast cell signaling and its role in urticaria. Annals of allergy, asthma, & immunology. 2024 Apr 1;
11. Diamanti A, Tontini C, Bulfone-Paus S. Comparing novel treatments in chronic spontaneous urticaria: A critical appraisal of Bruton's tyrosine kinase inhibitors versus anti-cytokine biologics in clinical trials. Clinical and Translational Allergy. 2025 Mar 27;15(4).
12. ClinicalTrials.gov. A phase 3 study of efficacy and safety of remibrutinib (LOU064) in adult patients with chronic spontaneous urticaria (REMIX-1). 2021 Sep 1 [cited 2026 Apr 21]. Available from: clinicaltrials.gov.
13. ClinicalTrials.gov. A phase 3 study of efficacy and safety of remibrutinib (REMIX-2) [Internet]. Bethesda (MD): National Library of Medicine (US); 2025 [cited 2026 Apr 21]. Available from: https://clinicaltrials.gov/study/NCT05032157.
14. Giménez-Arnau A, Ferrucci S, Ben-Shoshan M, Mikol V, Lucats L, Sun I, et al. Rilzabrutinib in Antihistamine-Refractory Chronic Spontaneous Urticaria: The RILECSU Phase 2 Randomized Clinical Trial. JAMA dermatology [Internet]. 2025 Autumn;e250733. Available from: https://pubmed.ncbi.nlm.nih.gov/40266575/
15. Metz M, Giménez-Arnau A, Hide M, Lebwohl M, Mosnaim G, Saini S, et al. Remibrutinib in Chronic Spontaneous Urticaria. New England Journal of Medicine. 2025 Mar 6;392(10):984–94.
16. Pavel Kolkhir, Fok JS, Emek Kocatürk, Li PH, Tiia-Linda Okas, Marcelino J, et al. Update on the Treatment of Chronic Spontaneous Urticaria. Drugs. 2025 Mar 12;
17. Metz M, Sussman G, Gagnon R, Staubach P, Tanus T, Yang WH, et al. Fenebrutinib in H1 antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. Nature Medicine [Internet]. 2021 Nov 1;27(11):1961–9. Available from: https://pubmed.ncbi.nlm.nih.gov/34750553/
18. Miyamoto K, Miller RM, Voors-Pette C, Oosterhaven JAF, van den Dobbelsteen M, Mihara K, et al. Safety, pharmacokinetics, and pharmacodynamics of sofnobrutinib, a novel non-covalent BTK inhibitor, in healthy subjects: First-in-human phase I study. Clinical and Translational Science. 2024 Nov;17(11).
19. Maurer M, Berger W, Giménez-Arnau A, Hayama K, Jain V, Reich A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. J Allergy Clin Immunol. 2022 Dec 1;150(6):1498-1506.e2. doi: 10.1016/j.jaci.2022.08.027.
20. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. Molecular Cancer [Internet]. 2018 Feb 19;17(1). Available from: https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-018-0779-z
21. Jain KK. Personalized Therapy of Cancer. Textbook of Personalized Medicine. 2015;199–381.
22. Roskoski R. Ibrutinib inhibition of Bruton protein-tyrosine kinase (BTK) in the treatment of B cell neoplasms. Pharmacological Research [Internet]. 2016 Nov [cited 2019 Jul 23];113:395–408. Available from: https://www.sciencedirect.com/science/article/pii/S1043661816309227
23. Galitzia A, Maccaferri M, Francesca Romana Mauro, Murru R, Marasca R. Chronic Lymphocytic Leukemia: Management of Adverse Events in the Era of Targeted Agents. Cancers. 2024 May 24;16(11):1996–6.

24. Lee DH, Hawk F, Seok K, Gliksman M, Emole J, Rhea IB, et al. Association between ibrutinib treatment and hypertension. Heart. 2021 Jul 1;108(6):445–50
25. Mendez-Ruiz A, Lossos IS, Cohen MG. Bleeding Risk With Antiplatelets and Bruton's Tyrosine Kinase Inhibitors in Patients With Percutaneous Coronary Intervention. Journal of the Society for Cardiovascular Angiography & Interventions. 2023 Mar 6;2(3):100608–8
26. Mihaela Andreescu. Risk of Infections Secondary to the Use of Targeted Therapies in Hematological Malignancies. Life. 2023 May 28;13(6):1272–2.
27. Boriani G, Menna P, Morgagni R, Minotti G, Vitolo M. Ibrutinib and Bruton's tyrosine kinase inhibitors in chronic lymphocytic leukemia: focus on atrial fibrillation and ventricular tachyarrhythmias/sudden cardiac death. Chemotherapy. 2022 Nov 10
28. Zhong Q, Zee K, Rasmussen K, McKinley BJ, Linger RMA, Ray SD. Side effects of anti-cancer medications. Side Effects of Drugs Annual. 2022;431–45.
29. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA2LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2021 Oct 20;77(3).
30. Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. Immunological Reviews. 2018 Feb 12;282(1):232–47.
31. Altrichter S, Fok JS, Jiao Q, Kolkhir P, Pyatilova P, Romero SM, et al. Total IgE as a Marker for Chronic Spontaneous Urticaria. Allergy, Asthma & Immunology Research. 2021;13(2):206.
32. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. Journal of Allergy and Clinical Immunology. 2018 Sep;142(3):876–82.
33. Angst D, Gessier F, Janser P, Vulpetti A, Wälchli R, Beerli C, et al. Discovery of LOU064 (Remibrutinib), a Potent and Highly Selective Covalent Inhibitor of Bruton's Tyrosine Kinase. Journal of Medicinal Chemistry [Internet]. 2020 May 28;63(10):5102–18. Available from: https://pubmed.ncbi.nlm.nih.gov/32083858/
34. Pulz R, Angst D, Cenni B. Next generation Bruton's tyrosine kinase inhibitors – characterization of in vitro potency and selectivity. European Journal of Pharmacology [Internet]. 2025 May 20;1002:177747. Available from: https://www.sciencedirect.com/science/article/pii/S0014299925005011
35. Sestier M, Hillis C, Fraser G, Leong D. Bruton's tyrosine kinase Inhibitors and Cardiotoxicity: More Than Just Atrial Fibrillation. Current Oncology Reports. 2021 Aug 3;23(10).
36. Saini S, Szalewski R, Gao X, Altrichter S, Haemmerle S, Seko N, et al. REMIX-1/-2: Early symptom improvements with remibrutinib in chronic spontaneous urticaria from week 1. Ann Allergy Asthma Immunol. 2024 Nov;133(6):S99.
37. Paydas S. Management of adverse effects/toxicity of ibrutinib. Crit Rev Oncol Hematol. 2019 Apr;136:56-63. doi: 10.1016/j.critrevonc.2019.02.001. Epub 2019 Feb 10. PMID: 30878129.
38. Spadafora L, Russo F, Bukowska-Olech E, Panichella G, Garofalo M, Cacciatore S, et al. Cardiovascular Safety of Bruton Tyrosine Kinase Inhibitors: From Ibrutinib to Next-Generation Agents. American Journal of Cardiovascular Drugs. 2025 Aug 28;26(1):21–34.
39. Rogers KA, Thompson PA, Allan JN, Coleman M, Sharman JP, Cheson BD, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica. 2021 Mar 18;106(9):2364–73.