



The Use of Bruton's Tyrosine Kinase Inhibitors to Treat Allergic Disorders

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Abstract

Purpose of review Studies show that inhibitors of Bruton's tyrosine kinase (BTKis), currently FDA-approved for the treatment of B cell malignancies, can prevent IgE-mediated reactions through broad inhibition of the FcεRI signaling pathway in human mast cells and basophils. This review will summarize recent data supporting the use of these drugs as novel therapies in various allergic disorders.

Recent findings Recent studies have shown that BTKis can prevent IgE-mediated degranulation and cytokine production in primary human mast cells and basophils. Two oral doses of the second-generation BTKi acalabrutinib can completely prevent moderate passive systemic anaphylaxis in humanized mice and even protect against death during severe anaphylaxis. Furthermore, two doses of ibrutinib can reduce or eliminate skin prick test responses to foods and aeroallergens in allergic subjects. BTKis in development also show efficacy in clinical trials for chronic urticaria. Unlike other therapies targeting IgE, such as omalizumab, BTKis appear to have rapid onset and transient effects, making them ideal candidates for intermittent use to prevent acute reactions such as IgE-mediated anaphylaxis.

Summary These studies suggest that BTKis may be capable of preventing IgE-mediated anaphylaxis, paving the way for future trials in food allergy and urticaria.

Introduction

The IgE pathway is a central pathogenic player in most allergic disorders, including food allergy, drug allergy, allergic rhinitis, asthma, and chronic urticaria. When allergen-specific IgE binds allergen, cross-linking high-

affinity receptors (FcεRI) on the surface of mast cells and basophils, the activated signaling cascade causes the release of numerous allergic mediators including histamine, prostaglandins, leukotrienes, and cytokines that are responsible for inducing signs and symptoms. In the past, the treatment of allergic disorders has largely depended on the blockade of specific mediators (e.g., with antihistamines or leukotriene receptor antagonists) and/or broad immune suppression with corticosteroids. More recently, IgE-targeting biologics including omalizumab have shown efficacy in reducing circulating IgE to improve urticaria and asthma, but they cannot completely suppress IgE-dependent mast cell and basophil activation. Therefore, there is an unmet need for therapies capable of preventing IgE-mediated allergic reactions. Recent studies suggest that drugs targeting Bruton's tyrosine kinase (BTK) might fill this need.

BTK is an essential kinase for signaling through FcεRI in human mast cells and basophils. Because it is also crucial for B cell maturation, BTK has been pharmacologically targeted for the treatment of B cell malignancies. There are now three FDA-approved BTK inhibitors (BTKis) in the USA. Ibrutinib (brand name Imbruvica®; manufacturers Janssen, Pharmacylics, and AbbVie),

acalabrutinib (Calquence®; Acerta and AstraZeneca), and zanubrutinib (Brukinsa®; BeiGene) are all oral, covalent small molecule inhibitors of BTK. They have rare serious side effects in patients taking them chronically for malignancies, including bleeding, cytopenias, cardiac arrhythmias, and infection, but they are generally well-tolerated [1–3]. As second-generation BTKis, acalabrutinib and zanubrutinib are more selective for BTK with fewer off-target effects compared to their predecessor, ibrutinib, and therefore have more favorable safety profiles [4–7]. Additionally, many BTKis in development are in clinical trials for the treatment of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus, raising the possibility that these next-generation BTKis could be safe enough for chronic use in non-malignant indications (Table 1) [8].

We and others have shown that clinically relevant concentrations of BTKis can prevent IgE-mediated degranulation and inflammatory cytokine production of human mast cells and basophils [9••, 10–12], suggesting that these drugs could be repurposed for the prevention of IgE-mediated reactions. This review will summarize recent data using BTKis in various allergic disorders.

Potential allergy indications

IgE-mediated anaphylaxis

One of the most exciting potential applications for BTKis is for the prevention of IgE-mediated anaphylaxis. Anaphylaxis is a possibly life-threatening systemic allergic reaction to substances such as foods, drugs, or stinging insect venoms. Despite efforts to mitigate allergies to these substances with immunotherapy, the prevalence of anaphylaxis is increasing [13]. Unfortunately, it is often fatal, even with prompt and comprehensive medical treatment [14]. There are no known therapies that can prevent IgE-mediated anaphylaxis, but recent work has shown promise for the use of BTKis to fill this niche.

Our lab has recently published studies showing that BTKis can prevent anaphylaxis in humanized mice *in vivo*. Due to functional redundancy of BTK with other kinases in the FcεRI pathway in murine cells [15, 16], BTK inhibition or knockdown is not sufficient to prevent IgE-mediated anaphylaxis in wild-type mice [17–20]. We therefore used humanized mice that can be engrafted with human leukocytes [9••]. NSG-SGM3 mice have transgenes for human stem cell factor, GM-CSF, and IL-3 on a highly immunodeficient background. When engrafted with human CD34+ cord blood cells, they support the expansion and maturation of human myelogenous cells including tissue mast cells and blood basophils. We found that just two oral doses of 15 mg/kg acalabrutinib given 16 and 4 h prior to intravenous antigen challenge completely prevented any observable clinical response during moderate passive

Table 1. BTK inhibitors on the market and in development. All listed BTKis are oral covalent inhibitors except where otherwise noted

Compound	Manufacturer/developer	Indications	Stage of development
Ibrutinib (Imbruvica®, PCI-32765)	Pharmacylics, Janssen, AbbVie	MCL ^a , CLL ^a , SLL ^a , MZL ^a , WM ^a , cGVHD ^a , severe COVID-19 infection	FDA-approved
Acalabrutinib (Calquence®, ACP-196)	Acerta Pharma, AstraZeneca	CLL ^a , MCL ^a , SLL ^a , severe COVID-19 infection	FDA-approved
Zanubrutinib (Brukinsa®, BGB-3111)	Beigene	MCL ^a , severe COVID-19 infection	FDA-approved
Abivertinib ^b (STI-5656)	Sorrento Therapeutics, Hangzhou ACEA Pharmaceutical	Non-small cell lung cancer, severe COVID-19 infection	Phase III
Evobrutinib (M2951)	Merck	Multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus	Phase III
PRN2246/SAR442168	Principia Biopharma/Sanofi	Multiple sclerosis	Phase III
Rizabrutinib ^c (PRN1008)	Principia Biopharma	Pemphigus, IgG4-related disease, ITP	Phase III
AC-0058TA	ACEA Biosciences	Systemic lupus erythematosus	Phase II
ARQ531	ArQule	B cell malignancies resistant to other BTKi's	Phase II
Branebrutinib (BMS-986195)	Bristol-Myers Squibb	Rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus	Phase II
CT-1530	Centaurus Biopharma Co	B cell malignancies	Phase I/II
DTRMWXHS-12	Zhejiang DTRM Biopharma	B cell malignancies	Phase II
DZD9008 ^b	Dizal Pharmaceuticals	Non-small cell lung cancer, NHL	Phase II
Elsubrutinib (ABBV-105)	AbbVie	Rheumatoid arthritis, systemic lupus erythematosus	Phase II
Fenebrutinib ^c (GDC-0853)	Genentech	CLL, chronic urticaria, diffuse large B cell lymphoma, systemic lupus erythematosus	Phase II
LOX0305 ^c	Loxo Oncology	B cell malignancies resistant to other BTKi's	Phase I/II
M7583	Merck	B cell malignancies	Phase I/II
Orelabrutinib (ICP-022)	Beijing InnoCare Pharma Tech	B cell malignancies, systemic lupus erythematosus	Phase I/II
Remibrutinib (LOU064)	Novartis	Atopic dermatitis, asthma, chronic urticaria, Sjogren's syndrome	Phase II
Tirabrutinib (ONO/GS-4059)	Ono Pharmaceuticals, Gilead	CLL, rheumatoid arthritis, Sjogren's syndrome	Phase II
Vecabrutinib ^c (SNS-062)	Sunesis Pharmaceuticals	B cell malignancies resistant to other BTKi's	Phase I/II
BIIB068 ^c	Biogen	Systemic lupus erythematosus	Phase I
BIIB091	Biogen	Multiple sclerosis	Phase I
CG-806 ^c	Aptose Biosciences	CLL, AML, NHL, SLL	Phase I

Table 1. (Continued)

Compound	Manufacturer/developer	Indications	Stage of development
HZ-A-018	Hangzhou HeZheng Pharmaceutical	B cell malignancies	Phase I
PRN473 ^{c,d}	Principia Biopharma/Sanofi	Autoimmune dermatologic disorders	Phase I
SN1011	SinoMab Pty	Autoimmune diseases	Phase I
TG-1701/SHR-1459	TG Therapeutics	CLL, NHL	Phase I

AML acute myeloid leukemia, *cGVHD* chronic graft versus host disease, *CLL* chronic lymphocytic leukemia, *EGFR* epidermal growth factor receptor, *ITP* immune thrombocytopenia, *MCL* mantle cell lymphoma, *MZL* marginal zone lymphoma, *NHL* non-Hodgkin's lymphoma, *SLE* systemic lupus erythematosus, *SLL* small lymphocytic lymphoma, *WM* Waldenström's macroglobulinemia
^aFDA-approved for this indication
^bDual selective inhibitor of EGFR and BTK
^cNoncovalent inhibitor
^dTopical formulation

systemic anaphylaxis (PSA) [9••]. Even more extraordinary was acalabrutinib's ability to significantly protect against death during severe PSA (13% mortality in mice pretreated with two doses of acalabrutinib compared to 39% mortality in mice pretreated with vehicle); mice treated with acalabrutinib also had a mitigated core body temperature drop and faster time to recovery during severe PSA (using a higher dose of antigen challenge) compared to mice treated with vehicle (-3.232 versus -4.179 °C, respectively). These findings are particularly impressive when considering the severity of the PSA model. Mice in these experiments were passively sensitized with only one specific IgE; thus their mast cells and basophils would be saturated with this one type of IgE rather than multiple different IgEs, as is the case for atopic humans. This, along with the intravenous antigen challenge route, produced a very robust (and often lethal) model of anaphylaxis. The 15 mg/kg dose of acalabrutinib used in these mice is equivalent to the FDA-approved 100 mg dose for humans in terms of pharmacodynamic activity and BTK occupancy [4]. This suggests that clinically relevant doses of BTKis may be protective against severe anaphylaxis in humans. Finally, the finding that BTKis can block IgE-mediated cytokine production in human primary skin-derived mast cells *in vitro* [9••] suggests that BTKis could also prevent the late phase of anaphylaxis, which is thought to be mediated by *de novo* cytokine production, though their effects on the late phase response have not yet been studied.

While BTKis have not yet been shown to prevent anaphylaxis in humans (clinical trials are ongoing in the author's laboratory), studies have demonstrated the ability of BTKis to reduce or eliminate skin prick test reactivity to aeroallergens and foods in allergic subjects. In the first pilot study, we investigated the hypothesis that ibrutinib would eliminate skin test reactivity to aeroallergens in cancer patients [10]. We enrolled patients who were prescribed standard FDA-approved doses of ibrutinib for their B cell malignancies and performed skin testing to a standard panel of aeroallergens at baseline (before ibrutinib treatment) and again 1 week after starting daily ibrutinib therapy. Though only two subjects were ultimately enrolled, both subjects had positive skin testing to aeroallergens (cat and ragweed for subjects #1 and 2, respectively) at baseline. One week after starting ibrutinib, both subjects' skin tests became negative. This was sustained 1 to 2 months later, while they were still on ibrutinib therapy. This pilot study paved the way for an open label clinical

trial investigating the effects of ibrutinib on skin prick test size and basophil activation testing in healthy food allergic adults ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03149315) identifier NCT03149315). In this trial, we recruited six healthy adults with confirmed IgE-mediated peanut and/or tree nut allergies [21••]. Four of the six subjects had a history of severe reaction after exposure to peanut or tree nuts, including anaphylaxis. Skin testing to clinically relevant foods ($n = 25$) was performed at baseline, and then subjects were given ibrutinib 420 mg orally once daily (an FDA-approved dose) for up to 7 days, returning during ibrutinib treatment for repeat skin testing. Remarkably, all 25 skin tests were reduced after just two doses of ibrutinib therapy compared to baseline, with a 77% average reduction of the wheal area. Overall, 44% of all skin tests became negative on ibrutinib. Though the effects of just one dose was not examined, additional doses of ibrutinib for up to 7 days did not show further suppression of skin tests compared to 2 days, suggesting that ibrutinib rapidly reached peak efficacy. Additionally, ex vivo IgE-mediated basophil activation testing for all subjects was completely suppressed while on ibrutinib therapy compared to baseline, in line with previously published data from ibrutinib's phase I clinical trial [22].

Both human and animal studies demonstrate rapid onset of action and transient efficacy of BTKis. In the clinical trials, the majority of skin tests and basophil activation had returned to baseline within 1 week after cessation of ibrutinib [21••]. In humanized mice, acalabrutinib was found to no longer significantly protect against PSA 2 days after dosing [9••]. We did not determine the precise duration of protection in either study; nonetheless, these findings confirm the temporary effect of BTKis that is also observed in human mast cells and basophils in vitro [9••]. The short duration of efficacy of these covalent inhibitors may give insight into the turnover rate for BTK in mast cells and basophils. While basophils rapidly and continuously regenerate from myeloid progenitors in the bone marrow, tissue-resident mast cells are thought to be long lived and slow to divide [23] and so must produce new BTK enzyme in order to overcome the effects of irreversible inhibitors. From a safety standpoint, this transient efficacy may even be beneficial if short courses of BTKis are used to prevent anaphylaxis to foods or drugs, both of which are discussed below.

Food allergy

If BTKis are shown to be protective against anaphylaxis, and especially if they are protective against fatal anaphylaxis, they may have potential for use in protecting against IgE-mediated food allergies, which can cause severe reactions including fatal anaphylaxis [14]. The most likely application for BTKis in food allergy is short-term use as adjuvant therapy for reducing the risks of adverse reactions during immunotherapy to foods. Food oral immunotherapy (OIT) has been shown in numerous trials to induce desensitization to foods in food-allergic patients [24, 25]. Palforzia®, a peanut-flour based OIT regimen, was recently the first food OIT product to receive FDA approval. Patients who can reach maintenance dose are generally protected against reactions due to accidental exposures for at least as long as they are taking OIT, though this desensitization does not typically persist after OIT cessation. Unfortunately, the doses of food OIT can themselves cause reactions, even anaphylaxis. Most adverse

reactions to food OIT occur during the build-up phase, and they can range from minor (urticaria or stomach upset) to severe (systemic anaphylaxis requiring treatment with epinephrine) [24–26]. Short courses of BTKis may be able to reduce the frequency and/or severity of adverse reactions during the build-up phase, allowing patients to safely reach maintenance dose. With their relatively short onset of action, BTKis may take the place of omalizumab, which has been shown to facilitate food OIT in trials, but, unfortunately, takes several months to take effect, and its protective effects against accidental food exposures are largely unknown [27, 28]. A major obstacle in using BTKis for food OIT is that food OIT is typically performed in children with food allergies, and younger patients may have more favorable and durable tolerance responses [29]. None of the currently FDA-approved BTKis have been tested in children, nor is the author aware of any safety data in children for any BTKi in development. Until these safety studies are done, it is unknown whether or not BTKis will be a viable option for use in aiding food OIT in children.

A less likely use for BTKis would be as chronic therapy to prevent reactions to foods. The aforementioned studies in humanized mice suggest that BTKis may have the ability to completely or partially prevent clinical reactivity to foods, but it is unknown if they would protect against mortality in the context of accidental exposure. Moreover, it is unclear if the benefits would outweigh the risks of chronic use (safety considerations for chronic use of BTKis are discussed below). Chronic systemic use of these drugs would have to have a favorable toxicity profile to warrant utilizing them long-term to treat allergic disorders. As discussed above, many BTKis in development are more selective for BTK and are seeking approval for autoimmune diseases. If they are safe enough for chronic use in autoimmune diseases, then they may also be safe enough to justify chronic use in food allergy to protect against accidental exposures, especially in patients whose food allergies are particularly severe and/or life threatening.

Drug allergy

In line with their use to prevent anaphylaxis, BTKis may also be utilized episodically in drug desensitizations. There are no approved therapies for drug allergy, though a desensitization may be considered if a medication is clinically essential. However, not only are desensitizations extremely labor-intensive and costly, but many hospitals and health centers do not perform them due to lack of resources such as an intensive care unit or an Allergy and Immunology consult service. If BTKis can reliably prevent IgE-mediated anaphylaxis, it is possible that they could reduce risk of adverse reactions during drug desensitizations, perhaps even to the point where desensitizations could be safely performed in any outpatient setting. It should be noted that BTKis would not likely prevent reactivity to drugs that cause IgE-independent allergy, such as cytokine release reactions from biologics or non-specific mast cell activation from iodinated contrast media, as BTK is not thought to be involved in these hypersensitivity reactions [30, 31]. Thus, BTKi use would be limited to preventing immediate hypersensitivity reactions due to medications that are known to have IgE-mediated mechanisms, such as beta-lactam antibiotics or platinum-based chemotherapy agents [32].

Chronic urticaria

The presence of circulating FcεRI-stimulating autoantibodies in a subset of chronic spontaneous urticaria (CSU) patients and the success of omalizumab in treating CSU suggests an FcεRI-mediated pathogenesis for chronic urticaria. To build on this hypothesis, several BTKis are now in clinical trials as potential therapies for CSU. Fenebrutinib (GDC-0853) is a highly selective noncovalent BTKi in development by Genentech [33, 34]. Phase IIa data from their multicenter, randomized controlled trial (NCT03137069) was recently released and showed promising efficacy in CSU [35••]. Adult subjects with antihistamine-refractory CSU were recruited and randomized to one of four arms: fenebrutinib 50 mg once daily, fenebrutinib 150 mg orally once daily, fenebrutinib 200 mg twice daily, or placebo for 8 weeks while continuing stable regimens of H1-antihistamines. The primary endpoint was a significant change in the Urticaria Activity Score Over 7 Days (UAS7) score (range: 0 to 42, with higher scores indicating higher disease activity) at week 8 compared to baseline. While the fenebrutinib 200 mg twice daily arm was the only group to achieve the primary endpoint, both this group and the 150 mg once daily treatment group showed marked clinical improvement compared to placebo, with changes in UAS7 scores of -21.8 and -17.1, respectively. Moreover, itch and hive scores showed rapid improvement in all treatment groups within 1 week of starting therapy and began to worsen again within 1 week of therapy cessation. Intriguingly, though subjects with auto-antibodies to FcεRI (termed “type IIb” autoimmunity in the trial) are known to be refractory to current CSU therapies including omalizumab, this subgroup had the quickest and most complete clinical response to fenebrutinib. These patients also showed a decrease in levels of auto-antibodies after 8 weeks of fenebrutinib therapy, though autoantibody levels were not analyzed at time points prior to 8 weeks. Overall, these data further support the hypothesis that FcεRI-dependent activation of mast cells and basophils plays a role in CSU.

One of the biggest obstacles that BTKis will face in CSU treatment is whether or not side effects during chronic use are acceptable. The major adverse event noted in fenebrutinib’s phase IIa trial was transient grade 3 elevations in ALT and/or AST in 8.3% and 6.3% of the subjects in the higher dose treatment arms (150mg once daily and 200 mg twice daily, respectively). This toxicity may prevent further trials for fenebrutinib in CSU. Liver toxicity does not appear to be a class effect of BTKis, raising hope that other BTKis may still gain approval, such as Novartis’ covalent BTKi remibrutinib (LOU064), which is currently in a phase IIb randomized controlled dose-finding trial for antihistamine-resistant CSU (NCT03926611) [36].

Other allergic disorders

The potential use of BTKis for other allergic indications remains uncertain. Candidate diseases would need to have an IgE-mediated mechanism, since BTK is not thought to be involved in other pathways of mast cell or basophil activation. For example, in mast cell disorders such as mastocytosis, idiopathic anaphylaxis, and idiopathic mast cell activation syndrome, it seems unlikely that BTKis would be effective if mast cell activation is triggered by IgE-independent pathways. Likewise, allergic asthma is a multi-factorial disease

with numerous cell types playing a pathologic role. Therefore, targeting the FcεRI pathway with a BTKi may not be fully efficacious. On the other hand, Principia Biopharma's topical BTKi in development (PRN473) may be a potential candidate for the treatment of allergic rhinitis and conjunctivitis if it has adequate penetration of mucosal surfaces. Topical application via nasal spray or eye drops may then avoid systemic toxicities that are associated with oral BTKis.

Safety and further considerations

Though congenital BTK deficiency, known as x-linked agammaglobulinemia (XLA), results in low or absent B cells and lack of humoral immunity [37], pharmacologic inhibition of BTK appears to be relatively well-tolerated. The most common side effects of the currently approved BTKis include nausea, diarrhea, rash, infection, cytopenias, bleeding, cardiac arrhythmias, and headache. Most side effects are mild and generally do not require treatment cessation or dose reduction [1–3, 38]. As most clinical trials have not reported toxicity data for periods shorter than 1 month of therapy, it is unknown whether or not these side effects would be mitigated with short-term use of a BTKi (e.g., for a few days). Our group was the first to publish safety data for brief use of a BTKi in healthy adults without cancer: we found no observable toxicity or side effects from up to 7 days of treatment with a standard dose of ibrutinib in adults with food allergy [21••]. No changes were detected in blood cell counts, kidney or liver function, quantitative immunoglobulin levels, or electrocardiogram during or after ibrutinib treatment compared to patients' baseline. While the study was small, it raises hope that BTKis may be used in short courses with minimal, if any, adverse effects.

Chronic use of BTKis for allergic disorders may have serious risks given the known side effect profiles of the currently FDA-approved BTKis. Notably, several of their side effects are thought to be due to off-target effects and, therefore, could theoretically be avoided by the use of a next-generation inhibitor with higher specificity for BTK. For example, even though BTK plays a role in platelet signaling and aggregation, XLA patients with congenital BTK deficiency are not at increased risk for bleeding. Patients taking ibrutinib, however, have an increased risk of bleeding during therapy, including major events such as gastrointestinal bleeding or subdural hematoma [39, 40]. Ibrutinib-related bleeding events may be caused, at least partially, by its off-target activity on TEC kinase. Acalabrutinib and zanubrutinib have minimal activity on TEC and have less frequent and less severe bleeding events compared to ibrutinib, though the frequent use of anticoagulants and antiplatelet agents in cancer patients complicates the assessment of true bleeding risk due to BTKis. Likewise, cardiac arrhythmias are another rare but serious side effect of all currently approved BTKis (most prevalent with ibrutinib) [1, 2, 41], but they are not seen in XLA. Fenebrutinib did not demonstrate bleeding or arrhythmia toxicities in its phase IIa trial [35••], further suggesting that these side effects are due to off-target effects and not directly due to BTK inhibition.

In contrast to their off-target effects, BTKis may have class-related adverse effects on immune function as a direct result of activity on BTK. In addition to

being a key kinase in the B cell receptor signaling pathway, BTK plays a pivotal role in innate immunity. It has been shown to be important for NLRP3 inflammasome activation, signaling through multiple Toll-like receptors, and inflammatory cytokine production in macrophages [42]. Some systematic analyses of clinical trials have concluded that cancer patients on chronic BTKi therapy (especially ibrutinib) have increased rates of infectious complications [43]. However, some analyses directly comparing BTKi treatment to placebo arms in phase III clinical trials have not found any such association [44]. Interestingly, the types of infections observed in patients taking BTKis differ from those seen in XLA patients. In XLA, the lack of B cell maturation results in global agammaglobulinemia, which renders patients susceptible to *Giardia lamblia* and bacterial infections, especially encapsulated bacteria [37, 45]. This infection risk is largely (though not completely) mitigated by correcting the underlying antibody deficiency using intravenous immunoglobulin therapy. With intact T cell responses, XLA patients can clear most viral and fungal infections. In contrast, patients taking BTKis chronically appear to be at increased risk for viral infections and invasive *Aspergillus* and *Cryptococcus* infections, with a median time to onset of about 4–6 months after starting BTKi therapy [43, 46]. The exact cause of this observation is unknown, but one possibility is that BTKis directly interfere with macrophage function and innate immune defense, resulting in susceptibility to opportunistic infections. Alternatively, pharmacologic BTK inhibition may merely exacerbate existing underlying immune dysfunction from B cell malignancies, either intrinsic dysfunction due to malignancy or iatrogenic dysfunction from prior treatment with multiple adjunct therapies including steroids, radiation therapy, and biologic and chemotherapy agents. Intriguingly, long-term follow-up studies from several ibrutinib trials now show that ibrutinib actually improves humoral immunity and cytopenias over the course of several years of therapy, suggesting that immune dysfunction is in fact a sequela of malignancy and not of BTKi treatment [47–49]. Finally, BTK inhibition may actually be protective in the setting of certain infections. Recent studies suggest that both XLA patients and cancer patients on chronic BTKi therapy are protected against complications from SARS-CoV-2 infection [50–52]. As a result of this observation, clinical trials are now underway utilizing ibrutinib, acalabrutinib, and zanubrutinib to treat severe cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19; NCT04439006, NCT04346199, and NCT04382586, respectively). Further studies will be needed to elucidate the real risk of infection with BTKi therapy, especially in healthy patients without cancer.

Resistance to BTKis has been reported after their chronic use in cancer patients [1]. During chronic treatment of malignancies such as CLL, B cells may acquire resistance to these drugs through mutations in the BTKi binding site in the kinase domain. It is possible that non-malignant cells such as normal mast cells could develop such resistance, but this seems unlikely unless there is both chronic exposure to BTKis and selective pressure (i.e., if BTK-dependent pathways are essential for mast cell survival). At this time, there is no evidence to suggest that BTKis deplete mast cells or otherwise stunt their maturation. Prior studies found that ibrutinib can reduce the survival and proliferation of canine mast cell lines and

canine neoplastic mast cells [53]; however, our own (unpublished) data found no differences in proliferation or survival of human skin-derived mast cells after treatment with ibrutinib, tirabrutinib, or acalabrutinib. In vivo data in food allergic adults and humanized mice demonstrate reversibility of BTKis' effects after short courses (up to seven days of treatment) [9••, 21••], suggesting that, at least during short-term use, BTKis are unlikely to affect mast cell survival in vivo.

Finally, it is unclear if the cost of the currently approved BTKis on the market would be prohibitive for their use in allergic indications. For episodic use, current pricing may not be an obstacle. Acalabrutinib costs around \$244 per dose (\$14,692 per month). If used in short courses to prevent anaphylaxis, two doses of acalabrutinib could considerably reduce the cost of food or drug desensitizations by offsetting expenses that would have otherwise resulted from ICU admission and/or the treatment of adverse reactions during the procedure. Conversely, chronic use of BTKis for allergic disorders at current pricing seems unlikely. However, there is hope that the BTKis that are in development for the treatment of chronic urticaria and autoimmune diseases may have substantially lower costs for long-term use compared to those used to treat cancers.

Conclusion

Because their onset of action is rapid and highly effective, and their duration of action is short, BTKis have several potential applications for short-term episodic use in allergic disorders with minimal toxicity, including food OIT and drug desensitizations. Their ability to prevent FcεRI signaling to all allergens is potentially paradigm shifting. Though many next-generation BTKis in development are targeting autoimmune disorders and other non-cancer indications, their safety profile with chronic use in healthy patients without cancer has yet to be determined. When these data become available, the safety and utility of using BTKis chronically to treat allergic disorders may be evaluated.

Declarations

Human and animal rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Conflict of interest

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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