



Potential applications of Bruton's tyrosine kinase inhibitors for the prevention of allergic reactions

Melanie C. Dispenza, Jennifer A. Regan & Bruce S. Bochner

To cite this article: Melanie C. Dispenza, Jennifer A. Regan & Bruce S. Bochner (2017) Potential applications of Bruton's tyrosine kinase inhibitors for the prevention of allergic reactions, Expert Review of Clinical Immunology, 13:10, 921-923, DOI: [10.1080/17446666X.2017.1370374](https://doi.org/10.1080/17446666X.2017.1370374)

To link to this article: <http://dx.doi.org/10.1080/17446666X.2017.1370374>



Accepted author version posted online: 22 Aug 2017.
Published online: 31 Aug 2017.



[Submit your article to this journal](#)



Article views: 98



[View related articles](#)



[View Crossmark data](#)

EDITORIAL



Potential applications of Bruton's tyrosine kinase inhibitors for the prevention of allergic reactions

Melanie C. Dispenza, Jennifer A. Regan and Bruce S. Bochner

Division of Allergy and Immunology, Northwestern University, Chicago, USA

ARTICLE HISTORY Received 10 July 2017; Accepted 18 August 2017

KEYWORDS Anaphylaxis; basophils; Bruton's tyrosine kinase (BTK); desensitization; hypersensitivity; ibrutinib; immunotherapy; mast cells

Anaphylaxis is a systemic allergic reaction to various substances including medications, foods, and stinging insect venom, characterized by acute onset of symptoms such as hives, angioedema, bronchospasm, nausea/vomiting, diarrhea, and/or hypotension. Currently there are no effective treatments capable of preventing anaphylaxis, and the mainstay of treatment is prevention by avoidance of triggers. However, strict avoidance is not always possible, especially in the case of food allergy, so standard of care consists of early recognition of signs and symptoms and the use of injected intramuscular epinephrine after a reaction has occurred [1]. In contrast, there are situations in which a patient is intentionally exposed to an allergen such as during skin testing, allergen immunotherapy (IT), and drug desensitizations, all procedures that carry a risk of a serious systemic reaction. Desensitizations to medications are expensive and labor-intensive, as these typically require inpatient admission due to the risk of potentially life-threatening reaction [2]. Subcutaneous IT to pollens and venom carries a small but real risk of anaphylaxis with each injection, especially in the build-up phase, so they must be administered under the direct care of a medical professional [3]. While currently there are no approved therapies for food allergy, several recently published clinical trials have demonstrated success in delivering oral and sublingual food proteins to induce a state of desensitization or sometimes even long-term tolerance [1,4–6]. Some trials have used rapid ('rush') desensitization protocols, which require inpatient hospitalization with rapid dose escalation over hours to days. As with the risks associated with IT to other substances, food IT also shows potential for significant and/or life-threatening adverse reactions, despite the fact that patients with a history of prior life-threatening reactions are excluded from enrollment in these trials. Recently, omalizumab (a humanized anti-IgE monoclonal antibody) has been shown in several studies to improve tolerability of rush food IT, but it needs to be started at least 8 weeks (or longer) prior to starting IT, proving it to be costly and not conducive to more urgent situations such as drug desensitizations [7]. Thus, there is an unmet need for therapies that can reduce the rate and/or severity of anaphylactic reactions in the context of accidental exposures as well as during desensitizations and IT.

Allergic anaphylaxis to foods, medications, and venom is mediated by allergens binding to IgE attached to high-affinity IgE receptors (FcεRI) on the surface of mast cells and basophils, thereby cross-linking these receptors, which in turn causes the rapid release of inflammatory mediators such as histamine, prostaglandins, leukotrienes, tryptase, and cytokines. Bruton's tyrosine kinase (BTK) is an enzyme that is located downstream of FcεRI and is essential for FcεRI-mediated activation of mast cells and basophils [8–11]. The importance of BTK in mediating systemic allergic responses is demonstrated by earlier studies showing that BTK deficient mice have impaired anaphylaxis in a model of passive cutaneous anaphylaxis (PCA) [12].

BTK is also located downstream of the B cell receptor and is important in B cell maturation, signaling, and function. Consequently, congenital BTK deficiency in humans results in X-linked agammaglobulinemia, a disorder characterized by low or absent numbers of circulating B cells and impaired humoral responses to infections. Due to the importance of BTK in B cell activation, pharmacologic inhibitors of BTK have been developed for the treatment of B cell lymphomas and leukemias. Currently there are only two BTK inhibitors that are FDA-approved for use in humans: ibrutinib (Imbruvica; Janssen Pharmaceuticals and Pharmacyclics Inc.) and dasatinib (Sprycel; Bristol-Myers Squibb). However, dasatinib, which was designed to primarily target the BCR/Abl kinase in Philadelphia chromosome positive leukemias, has meager BTK inhibiting activity compared to ibrutinib, and thus would be a poor choice for BTK targeting. There are several other BTK inhibitors in development, including (but not limited to) acalabrutinib (ACP-196; Acerta), ONO/GS-4059 (Ono Pharmaceuticals), BGB-3111 (BeiGene), and PRN1008 (Principia Biopharma Inc.), which are currently in clinical trials. Fortunately, pharmacologic inhibition of BTK appears to be clinically very different from congenital BTK deficiency, presumably because the bulk of B cell and plasma cell differentiation and maturation has already occurred before a BTK inhibitor would be used. Ibrutinib, which is an irreversible inhibitor of BTK, is very well tolerated, with the most common side effect being nausea or diarrhea. Very few patients stop taking ibrutinib due to side effects or toxicity, though serious side effects such as bone marrow suppression, bleeding, infection, cardiac arrhythmias,

and hypertension have been reported with chronic use in patients taking it for leukemia [13]. Some of the newer BTK inhibitors in development have higher specificity for BTK (e.g. acalabrutinib has no effect on EGFR or ITK), so they should have fewer side effects and better safety profiles from the standpoint of off-target effects [14]. Daily dosing appears to be necessary for inhibition of rapidly dividing B cells in the setting of lymphomas and leukemias. Mast cells, however, are long-lived and slow to divide in tissues. Thus, it may be possible to utilize BTK inhibitors to prevent allergic reactions in humans with minimal toxicity or inhibition of B cells, especially if used as short-term therapies in potentially life-threatening settings such as food or drug desensitizations. If safe and successful, such an approach could yield temporary 'mast cell stabilizing' pharmacologic properties with rapid onset that have long been sought-after.

Supporting this concept, Chang et al. showed that ibrutinib inhibits PCA in mice *in vivo*. Oral pretreatment (with doses similar to those tested in humans in clinical trials) partially inhibited allergen-mediated PCA. Notably, in some mouse models, the function of BTK in FcεRI signaling can overlap with other enzymes (e.g. interleukin-2-inducible T-cell kinase, known as ITK) such that BTK inhibition may not completely prevent FcεRI signaling in mouse cells [8,12]. Chang et al. also tested ibrutinib for its ability to prevent activation of culture-derived human mast cells *in vitro* [15]. Ibrutinib inhibited release of histamine and PGD₂ following FcεRI stimulation, but not after stimulation with fMLP or ionomycin (which activate non-BTK-dependent pathways), suggesting that its effect is mediated by selective inhibition of BTK in human mast cells. Ibrutinib also inhibited IgE-dependent release of TNF-α, IL-8, and MCP-1 (CCL2) from mast cells [15]. Additional studies using human basophils have also been promising. MacGlashan et al. showed that treatment of human basophils *in vitro* with ibrutinib inhibited IgE-mediated activation [9]. This was corroborated by data from the early clinical trials for ibrutinib, when Advani et al. showed that basophils from subjects taking ibrutinib for their lymphoproliferative disorders had diminished IgE-mediated activation *ex vivo* in as few as 4 h after the first ibrutinib dose [16]. This inhibition was still pronounced at 24 h after the first dose, though by this time IgE-mediated activation had partially recovered. These results provide encouragement for the concept that BTK inhibitors can inhibit or reduce the severity of anaphylactic reactions.

To date, there are no published studies that demonstrate the ability of BTK inhibitors to prevent anaphylaxis *in vivo* in humans, but our group has recently published a pilot study in patients with chronic lymphocytic leukemia (CLL) receiving ibrutinib to test the hypothesis that ibrutinib would eliminate allergic reactivity in adults with allergic rhinitis [17]. Enrolled subjects were prescribed ibrutinib as standard of care for their CLL. Each of the two subjects initially had a positive skin test to a single aeroallergen, either cat dander or ragweed pollen, in addition to a positive basophil activation test (BAT). Just 1 week after starting ibrutinib at 420 mg once daily, skin test wheal size was reduced to zero, and flare size was nearly eradicated, though responses to histamine, as expected, were unchanged. There was also a near complete inhibition of basophil activation as measured by the *ex vivo* anti-IgE-induced BAT, while non-IgE-mediated basophil

activation with fMLP, also as expected, showed little to no change. These effects were sustained for 1–2 months during continued ibrutinib therapy, the maximum time observed in this study. Allergen-specific IgE and total IgE were unchanged during this time; thus, it is likely that the diminished reactivity to allergens was a direct result of reduced activation and degranulation of mast cells in the skin due to BTK antagonism. In addition, we compared the potency and efficacy of ibrutinib versus acalabrutinib in the BAT *in vitro* using human whole blood samples. Dose-dependent inhibition was observed, with IC₅₀s of 40 and 105 nM, respectively, which are within the physiologic range for patients on ibrutinib therapy.

Our study, along with others, have set the stage for future efforts evaluating the potential episodic use of BTK inhibitors to enhance the safety and efficacy of IT and desensitizations, as well as for the prevention of anaphylactic reactions to foods and other substances. Given their excellent safety and tolerability profiles, it may also be possible to utilize BTK inhibitors on a more chronic basis for the treatment of other mast cell disorders where reactions are more frequent or unpredictable, such as idiopathic anaphylaxis, mast cell activation syndrome, and mastocytosis, if these disorders prove to be mediated by FcεRI or other BTK-dependent pathways.

Funding

This work was funded in part by a 2016 Dixon Translational Innovation Award to B.S. Bochner through the Northwestern University Clinical and Translational Sciences Institute and Northwestern Memorial Foundation, and the Northwestern University Allergy Immunology Research Program (NUAIR) T32 grant AI083216 from the National Institute of Allergy and Infectious Diseases to M.C. Dispenza.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol*. 2014 Nov;134(5):1016–25e43.
2. Liu A, Fanning L, Chong H, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy*. 2011 Dec;41(12):1679–1689.
3. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015 Nov;115(5):341–384.
4. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014 Feb;133(2):291–307. quiz 308.
5. Narisety SD, Frischmeyer-Guerrero PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol*. 2015 May;135(5):1275–82 e1–6.
6. Gorelik M, Narisety SD, Guerrero AL, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. *J Allergy Clin Immunol*. 2015 May;135(5):1283–1292.

7. Lin C, Lee IT, Sampath V, et al. Combining anti-IgE with oral immunotherapy. *Pediatr Allergy Immunol*. 2017 Aug 07. [Epub ahead of print]
8. Iyer AS, Morales JL, Huang W, et al. Absence of Tec family kinases interleukin-2 inducible T cell kinase (Itk) and Bruton's tyrosine kinase (Btk) severely impairs Fc epsilonRI-dependent mast cell responses. *J Biol Chem*. 2011 Mar 18;286(11):9503–9513.
9. MacGlashan D Jr., Honigberg LA, Smith A, et al. Inhibition of IgE-mediated secretion from human basophils with a highly selective Bruton's tyrosine kinase, Btk, inhibitor. *Int Immunopharmacol*. 2011 Apr;11(4):475–479.
- **This study was the first to show that treatment of human basophils *in vitro* with ibrutinib eliminates FcεR1-mediated activation.**
10. Kuehn HS, Swindle EJ, Kim MS, et al. The phosphoinositide 3-kinase-dependent activation of Btk is required for optimal eicosanoid production and generation of reactive oxygen species in antigen-stimulated mast cells. *J Immunology*. 2008 Dec 01;181(11):7706–7712.
11. Hendriks RW, Yuvaraj S, Kil LP. Targeting Bruton's tyrosine kinase in B cell malignancies. *Nat Rev Cancer*. 2014 Apr;14(4):219–232.
12. Hata D, Kawakami Y, Inagaki N, et al. Involvement of Bruton's tyrosine kinase in FcεpsilonRI-dependent mast cell degranulation and cytokine production. *J Exp Med*. 1998 Apr 20;187(8):1235–1247.
- **This paper was the first to show that BTK deficiency prevents anaphylaxis *in vivo* in mouse models of passive cutaneous anaphylaxis.**
13. Chavez JC, Sahakian E, Pinilla-Ibarz J. Ibrutinib: an evidence-based review of its potential in the treatment of advanced chronic lymphocytic leukemia. *Core Evid*. 2013;8:37–45.
14. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016 Jan 28;374(4):323–332.
15. Chang BY, Huang MM, Francesco M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. *Arthritis Res Ther*. 2011 Jul 13;13(4):R115.
- **This paper showed that pharmacologic inhibition of BTK with ibrutinib ameliorates anaphylaxis *in vivo* in mouse models of passive cutaneous anaphylaxis.**
16. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol: J Am Soc Clin Oncol*. 2013 Jan 01;31(1):88–94.
17. Regan JA, Cao Y, Dispenza MC, et al. Ibrutinib, a Bruton's tyrosine kinase inhibitor used for treatment of lymphoproliferative disorders, eliminates both aeroallergen skin test and basophil activation test reactivity. *J Allergy Clin Immunol*. 2017 Apr 04.[Epub ahead of print]
- **This is the first study to demonstrate that a BTK inhibitor (ibrutinib) can eliminate allergic reactivity in humans.**