Fenebrutinib and BTK inhibition: unveiling a new target for the treatment of chronic spontaneous urticaria

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Abstract

Fenebrutinib is an orally administered, selective and reversible BTK inhibitor. Metz et al recently published a double-blind, placebo-controlled, phase 2 trial where fenebrutinib (50mg daily, 150mg daily or 200mg twice-daily) or placebo were randomly administered to 93 adults with CSU refractory to up-dosed H $_1$-antihistamines during 8 weeks. Fenebrutinib was more effective than placebo in reducing weekly Urticaria Activity Score (UAS7) after 8 weeks, achieving rates of well-controlled disease (UAS7[?]6) of up to 57% (with a 200mg twice-daily dose).

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Chronic spontaneous urticaria (CSU) is defined by the presence of wheals with or without angioedema for more than six weeks, where no precipitating cause is identified.[1] Its physiopathology includes type I autoimmunity, with immunoglobulin E (IgE) autoantibodies against self-antigens, as well as type IIb autoimmunity, which involves the presence of IgG autoantibodies against IgE or the high-affinity IgE receptor, FcεRI.[2] H_1-antihistamines remain the first-line treatment of CSU. However, only 39% of these patients achieve control with standard doses.[3] Among those who are non-respondent, up-dosing H_1-antihistamines proves effective in 63% of patients. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, has been widely used to treat antihistamine-refractory CSU. A 2018 meta-analysis of 67 real-life studies of patients with CSU treated with omalizumab reported rates of complete and partial response of 72% and 18%, respectively.[4] However, there is a proportion of CSU patients who do not adequately respond to omalizumab, particularly those with features of type IIb autoimmunity.[5] This has led to a continued search for other potential targets for the treatment of CSU.

Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase activated by phosphorylation. It is found in myeloid cells, especially in B lymphocytes, and is essential to their development and differentiation.[6] In mast cells, BTK is involved in signaling following high-affinity binding of FcεRI to the Fc of a specific IgE. Phosphorylated BTK activates phospholipase Cγ1, resulting in increased cytoplasmic calcium levels, further signaling by Ras/Raf-1/MEK/ERK, and cytoskeletal actin rearrangement.[7] Fenebrutinib is an orally administered, selective and reversible BTK inhibitor. Metz et al recently published a double-blind, placebo-controlled, phase 2 trial where fenebrutinib (50mg daily, 150mg daily or 200mg twice-daily) or placebo were randomly administered to 93 adults with CSU refractory to up-dosed H_1-antihistamines during 8 weeks. Fenebrutinib was more effective than placebo in reducing weekly Urticaria Activity Score (UAS7) after 8 weeks, achieving rates of well-controlled disease (UAS7[?]6) of up to 57% (with a 200mg twice-daily dose).[8] Interestingly, this effect was similar at week 4 than at the 8-week endpoint (61% of well-controlled patients in the 200mg twice-daily group). In comparison, data from omalizumab clinical trials show a proportion of well-controlled urticaria between 37% and 51% four weeks after a single 300mg dose.[9] This early effectiveness observed with fenebrutinib could prove beneficial, as it would allow for more timely treatment reevaluations and decision-making. Fenebrutinib was effective as early as during the first week of treatment, with 39% of patients in the 200mg twice-daily group achieving a well-controlled state at this point.[8]

Furthermore, fenebrutinib was equally effective in patients with and without type IIb autoimmunity. Metz et al found that patients with a positive basophil histamine release assay (BHRA+) or positive anti-FcεRI IgG antibodies presented better improvement of UAS7 at lower doses (fenebrutinib 50mg, 150mg daily) compared to those without these features of autoimmunity.[8] This addresses the challenge of finding an effective therapeutic target in patients with type IIb autoimmunity, which are less likely to respond to omalizumab.[5] The oral route of administration of fenebrutinib also shows some advantages, such as the possibility of taking the drug at home. In addition, preclinical studies in mammalian blood found that fenebrutinib has high oral bioavailability as well as decreased plasma clearance compared to its intravenous administration, which may result in longer-lasting inhibition of BTK in the treatment of CSU.[10]

Overall, the study by Metz et al portrays fenebrutinib as a new, fast-acting and safe alternative in the treatment of CSU. Despite some limitations, such as its sample size and limited follow-up, this study opens the way to further investigation regarding fenebrutinib and other potential BTK inhibitors in CSU, preferably by comparing them side-by-side to omalizumab or other therapies. BTK shows promise as a therapeutic target in CSU, particularly in patients with type IIb autoimmnunity on which achieving control remains a challenge. It is time to not only phenotype but to endotype CSU for a more individualized treatment. This increased understanding will allow for the discovery of new molecular pathways that may become novel targets for CSU.

Conflicts of interest

The authors declare no conflicts of interest.

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