The Efficacy and Hazards of All Bruton's Tyrosine Kinase Inhibitors are the Same: No

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Opinion

What is the difference between "best in class" and "first in class"? A clever remark, a long and winding route, and a lot of creativity and experience Bruton's Tyrosine Kinase Inhibitors (BTKIs) are a new family of chemicals being studied for Multiple Sclerosis treatment (MS). B-cells and myeloid cells are both modulated by BTKIs, the latter through the Fc receptor. Because they are tiny molecules, they can pass the blood–brain barrier and impact microglia in the Central Nervous System (CNS), possibly addressing both neurodegenerative and inflammatory components of MS. Evobrutinib, fenebrutinib, and tolebrutinib are now in Phase III clinical trials for the treatment of relapsing and progressive MS; orelabrutinib is in a Phase II trial; and BIIB091 is in a Phase I trial. Evobrutinib. Fenebrutinib and BIIB091 are reversible, non-covalent agents, whereas tolebrutinib and orelabrutinib are irreversible, covalent BTKIs. There is reason to assume that a "best in class" molecule will emerge from among these medicines. We're just getting started, but we're already seeing differences in selectivity, Bruton's Tyrosine Kinase (BTK) inhibitory strength, binding methods, and CNS penetrance across medicines. As we look ahead along the long and winding road ahead, we expect these characteristics to translate into significant efficacy and safety differences in Phase III studies and, eventually, in real-world practise. To reduce off-target toxicity and the risk of adverse effects, BTKIs must be selective. BTKIs, unlike cell-depleting treatments, seldom elicit significant reductions in lymphocyte or immunoglobulin levels, and they are linked with low risks of secondary infection. However, cardiac arrhythmias, bleeding, hypertension, diarrhoea, arthralgias, and fungal infections have all been related to the first generation BTKI, ibrutinib, which was licenced for the treatment of B-cell malignancies in 2013. Ibrutinib's action on other kinases such Epidermal Growth Factor Receptor (EGFR) and Janus kinase 3 causes off-target effects (JAK3). With the more selective, second-generation BTKI, acalabrutinib, adverse effects were reduced but not eradicated, with haemorrhage, neutropenia, and fungal infections still being noted. The BTKIs being studied in MS are more selective, although they still show a variety of activity, with tolebrutinib binding the most other kinases and fenebrutinib and orelabrutinib being the most selective for BTK. Headaches, nasopharyngitis, and minor Liver Function Test (LFT) and lipase increases were among the most prevalent side events reported in Phase II trials with evobrutinib and tolebrutinib. However, given the small number of patients recruited and the short duration of these studies, we expect selectivity to result in diverse side effect profiles among therapies in Phase III trials and clinical practise, as we have seen with approved BTKIs. Furthermore, on-target BTK inhibition may be responsible for some significant side effects, at least in part. Inhibition of the BTK and TEC families, for example, is thought to cause secondary bleeding. Bleeding or bruising was recorded in 8% of patients in a pooled review of studies using fenebrutinib in various illnesses, while major bleeding events were rare. The mechanism of fungal infection is unknown; however it could be related to BTK inhibition's impact on the innate immune system. Previous experience with other MS medicines underlines the need for attention in the post-marketing age for uncommon but major adverse effects that may arise, further distinguishing BTKIs. Pharmacodynamics and kinetics will almost certainly be important in determining comparative efficacy. The potency of BTK inhibition differs amongst medications. In comparison to tolebrutinib and fenebrutinib, evobrutinib requires higher doses to attain half maximum Inhibitory Concentration (IC50). When compared to evobrutinib and tolebrutinib, fenebrutinib suppressed B-cells and myeloid cells more effectively in vitro. The binding mechanism could be crucial in terms of drug resistance. Mutations in cysteine 481, the binding site for covalent BTKIs, have been discovered in patients on ibrutinib who have relapsed cancer. Fenebrutinib may be less vulnerable to this hazard by avoiding cysteine 481 as a non-covalent agent. Preliminary research suggests that CNS penetration differs between BTKIs, with tolebrutinib having more penetration than evobrutinib and fenebrutinib. If CNS penetrance is found to be a critical factor in microglial response adaptability, there should be benefits in treating progressive MS. Tolebrutinib at 60 mg daily reduced the number of slowly developing lesions, which have been linked to activated microglia and disability accumulation in MS, according to an exploratory analysis from the Phase IIb trial. The ability to prevent disability progression remains the most unmet requirement in the MS treatment landscape, and the ability to satisfy this objective could be a defining feature of BTKIs. FENtrepid is a phase III trial comparing fenebrutinib to ocrelizumab in Primary Progressive Multiple Sclerosis (PPMS); PERSEUS is a phase III trial comparing tolebrutinib to placebo in PPMS; and HERCULES is a phase III trial comparing tolebrutinib to placebo in secondary progressive MS. Both evobrutinib and tolebrutinib significantly reduced new gadolinium-enhancing lesions in relapse MS Phase II clinical studies. Other outcomes like relapse rate and disability progression are too early to distinguish BTKIs in relapsing MS. Evobrutinib, fenebrutinib, and tolebrutinib will be compared to teriflunomide in separate Phase III, randomised, double-blind trials in relapse MS. Although recurrence rates cannot be directly compared between studies, the identical trial designs and active comparator arms may allow some inferences about comparative efficacy. More research is also needed to determine the efficacy and safety of BTKIs in elderly and non-white patients. Participants in the tolebrutinib and evobrutinib Phase II trials were 37 and 42 years old, respectively, with 92% in the tolebrutinib and evobrutinib trials. In the evobrutinib experiment, all of the participants were White. Will we find a door at the end of this long, winding path, as the Beatles would have wondered? Selectivity, BTK inhibition strength, binding methods, and CNS penetrance are all essential characteristics of BTKIs. With enough evidence and experience, we can hope to find a "best in class" molecule and a way into the CNS that will turn that long and meandering journey into a straight and steady path to MS progression treatment.

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