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All Bruton's tyrosine kinase inhibitors have similar efficacy and risks: No

Dalia L Rotstein

Correspondence to:
DL Rotstein
Multiple Sclerosis Clinic, St. Michael's Hospital, 30 Bond St., Toronto, ON M5B 1W8, Canada.
dalia.rotstein@unityhealth.to

Dalia L Rotstein
Department of Medicine, University of Toronto, Toronto, ON, Canada
Multiple Sclerosis Clinic, St. Michael's Hospital, Toronto, ON, Canada

What lies between "first in class" and "best in class"? A turn of phrase, a long and winding road, a wealth of innovation and experience. Bruton's tyrosine kinase inhibitors (BTKIs) are a novel class of molecules under investigation for treatment of multiple sclerosis (MS). BTKIs modulate both B-cells and myeloid cells, the latter through the Fcγ receptor. As small molecules, they can cross the blood–brain barrier and affect microglia in the central nervous system (CNS), thus offering the promise of potentially treating neurodegenerative aspects of MS as well as inflammatory activity. Individual agents currently in Phase III clinical trials for treatment of relapsing and progressive MS include evobrutinib, fenebrutinib, and tolebrutinib; in a Phase II trial, orelabrutinib; and in a Phase I trial, BIIB091. Evobrutinib, tolebrutinib, and orelabrutinib are all irreversible, covalent BTKIs, whereas fenebrutinib and BIIB091 are reversible, non-covalent agents.

There is good reason to believe that, among these therapies, a "best in class" molecule will emerge. We are only at the trailhead, but we already observe disparate selectivity, strength of Bruton's tyrosine kinase (BTK) inhibition, binding mechanisms, and CNS penetrance across drugs. As we peer down the long and winding road ahead, we anticipate these features will translate into meaningful efficacy and safety differences across Phase III trials and eventually in real-world practice.

Selectivity of BTKIs is essential to minimize off-target toxicity and potential for adverse events. Unlike cell depleting therapies, BTKIs rarely cause major reduction in lymphocytes or immunoglobulin levels and are associated with relatively low rates of secondary infection. However, the first generation BTKI, ibrutinib, approved for the treatment of B-cell malignancies in 2013, was linked to other concerning adverse events including cardiac arrhythmias, hemorrhage, hypertension, diarrhea, arthralgias, and fungal infections. Off-target effects of ibrutinib stem from its activity on other kinases such as epidermal growth factor receptor (EGFR) and Janus kinase 3 (JAK3). Adverse events were reduced, but not eliminated, with the more selective, second generation BTKI, acalabrutinib, with bleeding, neutropenia, and fungal infections still reported.

The BTKIs under investigation in MS are more selective, but continue to evince a range with tolebrutinib binding the greatest number of other kinases, and fenebrutinib and orelabrutinib being the most selective for BTK.[1] Safety data from Phase II trials of evobrutinib and tolebrutinib have been reassuring, with common adverse events including headaches, nasopharyngitis, and mild liver function test (LFT) and lipase elevations.[2,3] However, given the relatively small numbers enrolled and brief durations of these studies, we expect that in Phase III trials and clinical practice, selectivity will lead to differential side effect profiles among therapies, as we have seen with approved BTKIs.[1,4]

Moreover, certain serious adverse events may be at least in part due to on-target BTK inhibition. Secondary bleeding, for example, is thought to arise from both BTK and TEC family inhibition.[4] In a pooled analysis of studies of fenebrutinib in other diseases, bleeding or bruising was reported in 8%, although serious bleeding events were rare.[5] The mechanism for fungal infection is incompletely understood but may be due to effects of BTK inhibition on the innate immune system.[6] Previous experience with other MS drugs highlights need for vigilance for rare, but serious, adverse events that may emerge in the post-marketing era and further differentiate BTKIs.

Pharmacodynamics and kinetics are likely to play a crucial role in determining comparative efficacy. Strength of BTK inhibition varies across drugs. Greater concentrations of evobrutinib are required to achieve half maximal inhibitory concentration (IC50) compared to tolebrutinib and fenebrutinib.[7] When studied in vitro, fenebrutinib achieved greater suppression of B-cells and myeloid cells compared to evobrutinib and tolebrutinib.[8] Binding mechanism may prove critical to potential for drug resistance. Oncologists have identified mutations in cysteine

481, the binding pocket for covalent BTKIs, in patients on ibrutinib suffering cancer relapses.[9] By avoiding cysteine 481 as a non-covalent agent, fenebrutinib may prove less vulnerable to this threat.

There is preliminary evidence that CNS penetration varies across BTKIs, with tolebrutinib demonstrating greater penetrance compared to evobrutinib and fenebrutinib.[10] If degree of CNS penetrance proves key to adaptation of microglial responses, there would be expected advantages for treatment of progressive MS. In an exploratory analysis from the Phase IIb trial of tolebrutinib, tolebrutinib at 60 mg daily was found to reduce volume of slowly expanding lesions, which have been associated with activated microglia and disability accumulation in MS.[3]

Prevention of disability progression remains the greatest unmet need in the MS therapeutic landscape, and ability to meet this endpoint could prove a pivotal point of distinction among BTKIs. Phase III trials underway in progressive MS include FENtrepid, comparing fenebrutinib to ocrelizumab in primary progressive multiple sclerosis (PPMS); PERSEUS, comparing tolebrutinib to placebo in PPMS; and HERCULES, comparing tolebrutinib to placebo in secondary progressive MS.

In Phase II clinical trials in relapsing MS, both evobrutinib and tolebrutinib strongly reduced new gadolinium-enhancing lesions.[2,3] It is too early to distinguish BTKIs in relapsing MS on other endpoints such as relapse rate and disability progression. In separate Phase III, randomized, double-blind trials in relapsing MS, evobrutinib, fenebrutinib, and tolebrutinib will each be compared against teriflunomide. Although we cannot compare relapse rates directly across trials, the similar trial designs and parallel active comparator arms may allow for some inferences regarding comparative efficacy. In addition, further work is necessary to determine efficacy and safety of BTKIs in older and non-white patients. The mean age of participants in the tolebrutinib and evobrutinib Phase II trials was 37 and 42 years, respectively; 92% in the tolebrutinib and 100% in the evobrutinib trial were White.[2,3]

The Beatles might have asked: at the end of this long and winding road, will we find a door? BTKIs differ in important respects, including selectivity, strength of BTK inhibition, binding mechanisms, and CNS penetrance. We can expect that, with accumulating evidence and experience, we will arrive at a "best in class" molecule—and a door into the CNS—that will transform that long and winding road, perhaps, into a straight and steady path to treatment of progression in MS.

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ORCID iD

Dalia L Rotstein https://orcid.org/0000-0002-7280-3684

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All Bruton's tyrosine kinase inhibitors have similar efficacy and risks: Commentary

Özgür Yaldizli and Tobias Derfuss

Correspondence to:
T Derfuss
Department of Neurology, University Hospital Basel, University of Basel, Petersgraben 4, 4031 Basel, Switzerland.
tobias.derfuss@usb.ch

Özgür Yaldizli
Tobias Derfuss
Department of Neurology, University Hospital Basel, University of Basel, Basel, Switzerland

Multiple sclerosis (MS) is a complex disease with different clinical and pathological phenotypes, potentially reflecting even different pathways to tissue injury.[1] The central process in MS pathology is inflammation mediated by T- and B-cells triggering damage to axons and their myelin sheaths.[2] For a long time, it was thought that T-cells are the main culprits in MS. Surprisingly, the depletion of B-cells by anti-CD20 antibodies resulted in an impressive reduction of relapse rates in relapsing-remitting MS and mild reduction of disability progression in primary progressive MS which led to a new treatment approach.[3]

However, the depletion of B-cells is not the only way to inhibit the B-cell response. Bruton's tyrosine kinase (BTK) is a key molecule in B-cell signal transduction.[4] Blocking this enzyme does not induce B-cell depletion as in ocrelizumab-treated patients but inhibits the differentiation and the survival of B-cells *and* myeloid cells.[4] This results in a reduced and modified B-cell response.[4] In addition and this might become a game changer, BTK inhibitors are more than 300 times smaller than ocrelizumab.[5] They can pass the blood–brain barrier. Thus, the hope is that BTK inhibitors do not only inhibit the peripheral B-cell response in MS as ocrelizumab but also influence neuroinflammation and neurodegeneration within the central nervous system.

In this edition of *Controversies*, we discuss whether or not the BTK inhibitors that are currently investigated in clinical trials are the same with regard to efficacy or safety.

Rotstein presented important differences between the different BTK inhibitors with regard to the selectivity of the tyrosine kinase, the strength of enzyme inhibition, the differences in the binding mechanisms, and the ability to penetrate across the blood–brain barrier.[6]

It seems obvious to assume that differences in pharmacokinetics and pharmacodynamics between the different BTK inhibitors also lead to differences in drug efficacy and safety. It could be speculated that a less stringent target profile of a BTK inhibitor leads to a broader effect on different cell types increasing efficacy but this might of course also influence the side effect profile.

On the contrary, currently, there are no convincing data whether and if at all, these differences really translate into clinical practice.[7] Some side effects of BTK inhibitors like an increased bleeding risk might be class effects and might be seen with all compounds but in varying degrees as mentioned by Navas.[7]

To transfer safety data from oncology trials to MS patients is problematic for obvious reasons. We agree that indirect comparison of drug efficacy across randomized controlled trials is challenging as these trials study different patient populations.[6] However, there are techniques that may allow comparisons between the different studies and study populations such as propensity score weighting or other statistical methods.[8] We all are excited to see these data in the next years.

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