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Bruton's tyrosine kinase inhibitor for multiple sclerosis: new hope or false dawn

Neil P Robertson^{1*}

¹Institute of Psychological Medicine and Clinical Neuroscience, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, CF14 4XN UK

*Corresponding author

Introduction

Bruton's tyrosine kinase (BTK) is encoded by the BTK gene and plays a crucial role in B cell development. It is an intra-cellular signalling molecule involved in regulation of maturation, survival, migration, and activation of B cells and microglia, which are important components in the immunopathogenesis of multiple sclerosis (MS). Mutations in BTK are associated with primary immunodeficiency and BTK inhibitors (BTKi) have also been successfully deployed in the treatment of chronic myeloid leukaemia. BTK has also been linked to autoimmune disorders but use of BTKi have been held back because of off target toxicity. However, with the development of second generation BTKi, toxicity has been limited and their CNS penetrance has been an attractive property in treatment of neurological disease. As a result, they are being investigated in a range of autoimmune disorders including multiple sclerosis. Several clinical trials are now completed or nearing completion (Evobrutinib, Tolebrutinib, Remibrutinib and Fenebrutinib). In this month's journal club, we report on the first phase 3 trial to report in this field and reflect on efficacy, toxicity and mechanism of action.

Safety and efficacy of evobrutinib in relapsing multiple sclerosis (evolutionRMS1 and evolutionRMS2): two multicentre, randomised, double-blind, active-controlled, phase 3 trials.

These were 2 large multicentre, randomised, double-blind, double-dummy, active-controlled clinical trials aiming to explore the efficacy and safety of evobrutinib compared to teriflunomide. Inclusion criteria included age 18-55, diagnosis of relapsing MS and disability as measured by the expanded disability score status (EDSS) of 0.0-5.5. Participants were randomly allocated to either Tolebrutinib 45mg twice a day or teriflunomide 14mg od with respective dummy medications. Primary end point was annual relapse rates up to 156 weeks. 2290 participants in total were randomised and used in primary analysis (1124 in evolutionRMS1 and 1166 in evolutionRMS2) stratified by geographical region and EDSS.

Annualised relapse rate was 0.15 (95% CI 0.12-0.18 with evobrutinib vs 0.14 [0.11-0.18] with teriflunomide (adjusted RR 1.02 [0.75-1.39]; p=0.55) in evolutionRMS1 and 0.11 (0.09-0.13 vs 0.11 [0.09-0.13]; adjusted RR 1.00 [0.74-1.35]; p=0.51) in evolutionRMS2. Although the proportion of treatment-emergent adverse events were balanced across the groups, serious TEAE were more common in the evobrutinib group. In particular, raised liver enzymes of at least 5 times normal occurred in 5% of the evobrutinib group compared to <1% in the teriflunomide group.

Comment: Whilst clearly a disappointing result in terms of non-superiority to teriflunomide, the incidence of drug related liver injury has raised significant safety concerns, so that

evobrutinib is unlikely to progress further as a treatment for relapsing MS. However, some biological effects of BTKi may make them a more natural treatment for aspects of progressive disease and these trials are on-going. It has also been reported that an extension of the original phase 2 study showed continuing efficacy on clinical and MRI measures up to 48 weeks at 75mg twice a day and a re-evaluation of dose may be considered. It will also be important in other trials of BTKi to see if the markedly raised liver enzymes in the first 12 weeks of treatment is a class or drug specific effect. If a class effect and shown to have efficacy in progressive disease, it is likely that there will be a higher bar for any licencing and a strict monitoring regime for a period after first dose.

Montalban X, et al. Lancet Neurol. 2024 Nov;23(11):1119-1132. doi: 10.1016/S1474-4422(24)00328-4. Epub 2024 Sep 19. PMID: 39307151.

BTK regulates microglial function and neuroinflammation in human stem cell models and mouse models of multiple sclerosis.

Whilst the winds of time have favoured first T cell then B cell mediated pathology as a primary driving factor in disease pathology, attention has more recently turned to the involvement of microglia as the predominant innate immune system of the central nervous system. They are found in the active border of chronic active lesions, thought to be an important process in progressive disability accumulation. BTKi target both adaptive and innate pathological processes so that the potential to target both B cells and microglia with a molecule that passes easily over the blood brain barrier and to understand their effect on inflammatory processes is a subject of considerable interest.

In this study the MOG35–55 peptide induction EAE model of MS was used to determine if a small molecule CNS penetrant BTKi was able to attenuate disease manifestations. Clinical scores were significantly improved in animals treated with small molecule BTKi, partially improved with non-CNS penetrant BTKi (suggesting some peripheral mechanistic component) and were unaffected by anti-CD20 administration. The investigators also identified a broad but specific transcriptomic anti-inflammatory signature for BTK inhibition across in vitro mouse and human cellular models involving 253 genes.

The authors then used a mouse microglial cell line with detectable phosphorylated BTK in vitro to explore cellular pathways. By stimulating microglia with IgG they demonstrated increased BTK phosphorylation which was partially blocked with tolebrutinib including pathways involved in neuroinflammation and autoinflammation. Similar experiments using human induced pluripotent stem cell derived microglia, neurons and astrocytes revealed a clear BTK gene expression signature focussed on microglia which they propose influences neuronal and astroglial signalling.

Finally, BTK, mRNA and protein levels were explored in postmortem tissue from progressive MS patients. BTK was increased in demyelinating regions and the BTK dependent genes previously identified from the in vitro models clearly segregated progressive MS lesions from that of normal appearing white matter.

Comment: These important studies highlight the importance of BTKi across a wide range of CNS cells including B cells and microglia. They also provide further support for the rationale in developing this class of drugs to beneficially modify pathology in multiple sclerosis and have the important added benefit of being CNS penetrant. An improved understanding of underlying cellular mechanisms may also allow a more focussed indication for their use.

Gruber RC et al. Nat Commun. 2024 Nov 22;15(1):10116. doi: 10.1038/s41467-024-54430-8. PMID: 39578444; PMCID: PMC11584639.

Summary: The first of several phase 3 trials examining efficacy in relapsing MS has not been able to demonstrate a significant benefit and has also raised important safety concerns. More results are on their way and it will be important to understand whether the safety signals identified are drug or class specific and whether other BTKi also fail to reach their endpoints for relapsing MS. However, as has been reported in preliminary data for another BTKi, it may be that they will have more of a role in progressive disease as is hinted by the unravelling of relevant molecular mechanisms and pathways.