Effects of evobrutinib, a Bruton's tyrosine kinase inhibitor, on slowly expanding lesions: an emerging imaging marker of chronic tissue loss in multiple sclerosis

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Abstract

Introduction: Slowly expanding lesions (SELs) are chronically active, demyelinated MS lesions, likely driven by sustained microglia/macrophage activity, resulting in irreversible neural tissue damage and axonal loss. Evobrutinib, a highly selective Bruton's tyrosine kinase inhibitor (BTKi), targets B cells, macrophages, and microglia. In a phase II trial (NCT02975349) in patients with relapsing MS, evobrutinib 75mg twice-daily (BID) reduced T1 gadolinium-enhancing lesions (Week 24) vs placebo.

Objective: To evaluate the effect of evobrutinib treatment vs comparator on SEL volume from baseline to Week 48.

Methods: SELs were identified, via MRI, as radially expanding areas of pre-existing T2 lesions of ≥10 contiguous voxels (size ~30mm^3). Analysis of SEL volume, stratified by baseline T2 lesion volume tertiles, was based on Week 48/end-of-treatment values (completers and discontinuers); treatment effect was analyzed via stratified Hodges-Lehman estimate of distribution shift and stratified Wilcoxon rank sum test. Evobrutinib dose groups (25mg QD, n=50; 75mg QD, n=51; 75mg BID, n=53) were compared with placebo/evobrutinib 25mg QD (n=53). Pooled groups (evobrutinib high doses [HD; 75mg QD and BID] vs low dose [LD; placebo and evobrutinib 25mg QD]) were used for subgroup analyses.

Results: Relative to the comparator, SEL volume decreased with increasing evobrutinib dose (25mg QD, -136.5mm^3 [95% CI: -618.0, 309.0], p=0.505; 75mg QD, -246.0mm^3 [-712.0, 97.0], p=0.192; 75mg BID, -474.5mm^3 [-1098.0, -3.0], p=0.047). SEL volume was significantly reduced for evobrutinib HD vs LD within the following subgroups: baseline EDSS ≥3.5 (n=55, -652.0mm^3 [95% CI: -1507.0, -100.0], p=0.020), relapsing-remitting MS (n=89, -317.0 mm^3 [-731.5, -29.0], p=0.025) and longer disease duration (≥8.5 years; n=44, -729.3mm^3 [-1706.5, -20.0], p=0.040).

Conclusions: Evobrutinib reduces SEL volume in a dose-dependent manner in relapsing MS and is especially apparent in more advanced disease. This is the first evidence that a BTKi impacts brain lesions associated with chronic inflammation and tissue loss, probably via microglia.

Disclosures:

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