Effect of evobrutinib, a Bruton's tyrosine kinase inhibitor, on immune cell and immunoglobulin levels over 48 weeks in a phase 2 study in relapsing multiple sclerosis

Short title: Evobrutinib and immune cell/Ig levels in MS

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Background: Evobrutinib, a highly selective Bruton's tyrosine kinase (BTK) inhibitor, with a multimodal mechanism of action impacting both B cells and macrophages, is the first BTK inhibitor to demonstrate clinical efficacy in multiple sclerosis (MS) in a Phase 2 study (NCT02975349) [1]. The effect of evobrutinib on immune cells and immunoglobulins (Ig) was investigated.

Methods: Adults with relapsing MS were randomized to double-blind evobrutinib 25mg QD, 75mg QD, 75mg BID, placebo, or open-label dimethyl fumarate 240mg (reference). Placebo-treated patients switched to evobrutinib 25mg QD at Week 24. Safety of evobrutinib, including assessment of B cell numbers and Ig levels, was a key secondary endpoint; investigations of effect on B cell subsets, T cell subsets, and natural killer (NK) cells in peripheral blood over 48 weeks were exploratory.

Results: Of 267 patients randomized, 227 completed 48 weeks' treatment. Over 48 weeks, there were no clinically relevant changes in number of total B cells, or of memory B, mature-naïve B, total T, helper T, cytotoxic T, or NK cells in any evobrutinib group and no changes in IgG or IgG subtype levels in any group. At Week 48, there were slight increases from baseline in IgA, and reductions in IgM, for all evobrutinib groups that were numerically greater than those with placebo at Week 24.

Conclusions: MS patients treated with evobrutinib showed no evidence of B cell depletion or changes in B cell subsets over 48 weeks. IgG levels remained stable and slight elevations in IgA and reductions in IgM levels were observed with evobrutinib. These findings demonstrate that, in contrast to genetic deletion of BTK, continued pharmacological BTK inhibition does not lead to B cell depletion or significant reductions in circulating immunoglobulins over 48 weeks.

1. Montalban et al. N Engl J Med 2019;380:2406–19.

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