Ocrelizumab vs. Placebo in Primary Progressive Multiple Sclerosis (ORATORIO)

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Primary progressive MS (PPMS) accounts for 10-15% of all cases of MS, and is characterized by the gradual and progressive worsening of neurologic disability over time. At the time of this trial, there were no approved, disease-modifying therapies for PPMS, though from a pathophysiologic standpoint, B-cells were known to contribute to the pathogenesis of MS, possibly also PPMS, through various immune mechanisms. As such, targeting B-cell activity by way of monoclonal antibodies to the B-cell specific, CD20 receptor (i.e, via Rituximab, Ocrelizumab) was considered for PPMS and studied, specifically, in a previous phase 2-3 trial named OLYMPUS. OLYMPUS assessed the efficacy of Rituximab for PPMS, and although the primary efficacy endpoint was not met, subgroup analyses suggested a benefit for some PPMS patients. As such, this prior data served as the rationale for this phase 3 study evaluating the efficacy of Ocrelizumab for PPMS.

Experimental design and statistics: This was a randomized, parallel-group, placebo-controlled, double-blind study. Inclusion criteria included age 18-55yrs, a diagnosis of PPMS, an EDSS of 3.0-6.5, a score of $\geq$2 on the pyramidal functions component of the Functional Systems Scale, a pre-specified MS duration based on EDSS scores, and a known elevation of the CSF IgG index or at least 1 OCB in the CSF. Exclusion criteria are below.[1] Enrolled patients were randomly assigned in a 2:1 fashion to receive either Ocrelizumab (600mg) or placebo, every 24wks. The trial was event-driven, in that treatments were administered for a minimum of 5 doses (120wks) until the occurrence of 253 disability progression events within the full trial cohort. An investigator blinded to treatment group performed EDSS assessments and neurologic exams, and MRIs were evaluated by a blinded staff member. The primary efficacy endpoint was the % of patients with disability progression from baseline, sustained for $\geq$12wks[2]. Additional secondary efficacy endpoints were also evaluated in the following order: 1) disability progression at 24wks, 2) change in timed walk test scores, 3) brain volume changes, 4) brain lesion changes, and 5) changes in QOL. Drug safety and adverse events were also assessed. Statistically, data were analyzed using an intention-to-treat protocol and via log-rank tests, hazard ratios, ANCOVAs, and mixed-model repeated measures where appropriate.

Results: A total of 732 patients were randomized, with 488 to Ocrelizumab and 244 to placebo; baseline characteristics were similar (**Table 1**). The median trial duration was 2.9 and 2.8 yrs for the Ocrelizumab and placebo groups, respectively, until the designated clinical cutoff. In terms of the primary outcome, the % of patients with 12wk disability progression was 32.9% w/Ocrelizumab vs. 39.3% w/placebo (HR: 0.76, p = 0.03, **Fig 1A**). Further, secondary endpoint analyses also suggested the efficacy of Ocrelizumab, with a lower % of patients showing 24wk disability progression w/Ocrelizumab (29.6%) vs. placebo (35.7%, HR: 0.75, p = 0.04, **Fig 1B**), and better performance (vs. baseline) on the timed 25ft walk test (see **Table 2**). In terms of imaging analyses, the total volume of hyperintense T2 lesions on MRI, from baseline to 120wks, decreased with Ocrelizumab (-3.4%) but increased with placebo (+7.4%, p < 0.01, **Fig 2A**), and the reduction in total brain volume from baseline was also lower with Ocrelizumab vs. placebo (-0.9% vs. -1.09%; p = 0.02, **Fig 2B**). Finally, safety and adverse effect analyses demonstrated that the most common adverse effect of Ocrelizumab was a non-fatal infusion-related reaction, both URI + oral

[1] Exclusion criteria: h/o RRMS, PRMS, or SPMS, contraindications to MRI or glucocorticoids, prior use of B-cell depleting therapy

[2] Progression of disability: EDSS increase by 1pt if baseline was $\leq$5.5 or by 0.5pts if baseline was $\geq$5.5

herpes infections were more common w/Ocrelizumab, and more systemic neoplasms, overall, were reported w/Ocrelizumab vs. placebo (2.3% vs. 0.8%, respectively, **Table 3**).

Conclusions: Overall, data from this study demonstrated the efficacy of Ocrelizumab for PPMS, as both the primary efficacy endpoint as well as 4 of the 5 secondary efficacy endpoints were met with statistical significance. Further, safety analyses suggested no significant adverse effects of Ocrelizumab treatment in PPMS, though the etiology underlying the higher incidence of neoplasms w/Ocrelizumab was not clear. The authors noted that additional evaluation into this mechanism was warranted (i.e., if related to an anti-CD20 mechanism), and this study was followed later by an open-label extension phase, during which additional safety monitoring was planned. Regardless, the data herein suggested both the involvement of B-cells in the pathogenesis of PPMS, as well as the efficacy of Ocrelizumab in reducing or slowing disability progression in PPMS, at least in the select patient population studied here.

Summary created by Elaine Sinclair, D.O.