Abstract title: Exposure-Response Analyses of Ocrelizumab in Patients With Multiple Sclerosis

Short title: Ocrelizumab Exposure-Response in MS Patients

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Introduction

Ocrelizumab is a $CD20^+$ B-cell–selective monoclonal antibody approved for treatment of relapsing multiple sclerosis (RMS) and primary progressive MS (PPMS).

Objective

To describe the population exposure-efficacy/safety relationships of ocrelizumab in patients with multiple sclerosis.

Methods

Ocrelizumab Phase III data were analysed by exposure quartile to assess exposure-response relationships for clinical efficacy (annualised relapse rate [ARR], 24-week confirmed disability progression [CDP], MRI outcomes, B-cell depletion) and safety parameters. The relationship between circulating B-cell levels and CDP was assessed. Exposure quartiles were generated from a two-compartment population-pharmacokinetic model of ocrelizumab Phase II/III data with time-dependent clearance and body weight as the main covariate.

Results

Ocrelizumab reduced T1 gadolinium-enhancing and new/enlarging T2 MRI lesion counts to nearly undetectable levels in patients with RMS and PPMS and reduced ARR in patients with RMS to low levels (0.13-0.18) across all quartiles. Ocrelizumab's effect on CDP was exposure-dependent in patients with RMS (quartile 1-4 hazard ratios and 95% confidence intervals [95% CIs]: 0.70 [0.41-1.19], 0.85 [0.52-1.39], 0.47 [0.25-0.87] and 0.34 [0.17-0.70] versus interferon-beta 1a, respectively) and PPMS (quartile 1-4 hazard ratios [95% CIs]: 0.88 [0.59-1.30], 0.86 [0.60-1.25], 0.77 [0.52-1.14] and 0.55 [0.36-0.83] versus placebo, respectively). Higher ocrelizumab exposure led to lower median B-cell levels in patients with RMS and PPMS. Lower median B-cell levels in patients with RMS were associated with lower rates of CDP; no association in patients with PPMS was demonstrated. Safety parameters were similar across exposure quartiles.

Conclusions

Higher ocrelizumab exposure was associated with a greater risk reduction in CDP (RMS and PPMS). A greater depletion of circulating B-cells was demonstrated in RMS. Clinical and imaging benefits on ARR and MRI activity were independent of exposure (potential ceiling effect). A greater effect on CDP with higher exposure suggests that higher ocrelizumab exposure is important for an improved control of disability progression.

Disclosures

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