Pharmacokinetics, Pharmacodynamics and Exposure-Response Analyses of Ocrelizumab in Patients With Multiple Sclerosis

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Objective:
To describe the population pharmacokinetics, pharmacodynamics, and exposure-efficacy/safety relationships of ocrelizumab in patients with multiple sclerosis (MS).

Background:
Ocrelizumab is a CD20+ B cell-selective monoclonal antibody approved for treatment of relapsing MS (RMS) and primary progressive MS (PPMS).

Design/Methods:
Ocrelizumab Phase II/III data were analyzed using a non-linear mixed-effects model to describe ocrelizumab pharmacokinetics and assess covariate effects. Exposure-response relationships for clinical efficacy (annualised relapse rate [ARR], 12-/24-week confirmed disability progression [CDP]) and safety parameters (serious adverse events, serious infections, infusion related reactions) were assessed.

Results:
A two-compartment model with time-dependent clearance and body weight as main covariate described accurately ocrelizumab pharmacokinetics in patients with RMS (N=941) and PPMS (N=482). Exposure (area under the serum concentration–time curve) was 26% higher in patients with RMS <60kg and 21% lower in those >90kg versus a 75kg reference patient. Blood B-cell depletion correlated with ocrelizumab exposure. Patients with RMS obtained similar benefit with regards to ARR independent of exposure, however, risk reductions in 12-/24-week CDP was exposure-dependent in patients with RMS (12-week CDP hazard ratios by exposure quartile 1–4: 0.77, 0.80, 0.45 and 0.33 versus interferon-beta 1a, respectively) and PPMS (12-week CDP hazard ratios by exposure quartile 1–4: 0.87, 0.83, 0.78 and 0.59 versus placebo, respectively). All safety parameters assessed were similar across the exposure quartiles.

Conclusions:
Higher ocrelizumab exposure led to greater B-cell depletion. Clinical benefit on ARR was independent of exposure, but greater risk reduction in CDP was observed with higher ocrelizumab exposure in patients with RMS and PPMS, suggesting that higher ocrelizumab exposure (and greater B-cell depletion) is important for control of disability progression. The fact that effects are more pronounced in patients in higher exposure groups indicates that the current approved dose is closer to the lower part of the dose-response curve. The safety profile was similar across all exposure quartiles.