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POPULATION PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS OF EMAPALUMAB IN PATIENTS WITH MACROPHAGE ACTIVATION SYNDROME ASSOCIATED WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: Macrophage activation syndrome (MAS) is a rare, life-threatening complication of rheumatic diseases that occurs most frequently in patients with Still's disease (systemic juvenile idiopathic arthritis [sJIA] and adult-onset Still's disease [AOSD]). MAS is characterized by overproduction of interferon γ (IFNγ) and other cytokines. Emapalumab, a fully human anti-IFNγ monoclonal antibody, is being investigated as a treatment for patients with MAS in rheumatic diseases.
Objectives: To develop a population pharmacokinetic (PK)/pharmacodynamic (PD) model to describe the PD effect of emapalumab in patients with MAS associated with sJIA/AOSD.
Methods: A PK model was developed using pooled data from 3 studies (n=58; 2709 samples): (i) an open-label, single-arm, phase 2/3 clinical trial of 45 patients who received emapalumab for primary haemophagocytic lymphohistiocytosis; (ii) a pilot, open-label, single-arm, phase 2 study of 14 patients who received emapalumab for MAS in sJIA; and a 1-year, long-term, follow-up study of patients from both studies. PK analysis was performed using nonlinear mixed effects modelling (NONMEM® version 7.5). Three linked PK/PD models were then developed on data from the 14 patients in study (ii) to characterize the relationship between emapalumab exposure and laboratory parameters associated with MAS, namely C-X-C motif chemokine ligand 9 (CXCL9), soluble interleukin-2 receptor alpha (sIL-2Rα), and ferritin. These PD parameters and their treatment-induced changes were characterized by turnover models. Parameters were assumed to be in steady-state at baseline with exposure-induced inhibition after treatment start. Predictive performance of the model was assessed using goodness-of-fit (GOF) plots and visual predictive checks (VPCs).

Results: Emapalumab PK was adequately described by a two-compartment model with first-order elimination that was constant at total IFNγ concentrations <~10^4 pg/mL. Emapalumab clearance increased proportionally with total IFNγ concentrations. Estimated baseline levels of CXCL9, sIL-2Rα, and ferritin were 8400 ng/L, 6550 ng/L, and 15300 mg/L, respectively. A rapid PD response to changes in emapalumab concentration was observed. Emapalumab almost completely suppressed CXCL9, sIL2-Rα, and ferritin production (estimated reduction in synthesis rate: 98.3%, 87%, and 99.6%, respectively). Standard errors of all parameters obtained by a bootstrap procedure were <40% of their respective bootstrap means indicating good model precision. GOF plots and VPCs indicated good alignment between model predictions and observed concentrations for all parameters.
Conclusion: Population PK/PD modelling indicated that emapalumab rapidly suppresses CXCL9, sIL2-Rα, and ferritin production in patients with MAS associated with sJIA/AOSD.
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Patient Consent: Not applicable (there are no patient data)
Disclosure of Interest: P. Brossard Employee with: Sobi, A. Facius Consultant with: Sobi