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Population PK and exposure-response analyses supported the first approval of rituximab in pediatrics with Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA).

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Introduction: Rituximab (Rituxan/MabThera®, RTX), an anti-CD20 monoclonal antibody (mAb), is approved for treating adults with GPA and MPA (systemic autoimmune conditions affecting blood vessels) based on the results of RAVE (Induction) and Mainritsan (Maintenance) trials. This work reports the modeling work that supported a full extrapolation strategy from adults to pediatrics[1].

Methods: A population PK model developed in 122 adults from RAVE was updated with data from 25 pediatric patients from Study PePRS who received at least 4 weekly RTX IV doses of 375 mg/m^2.

Cumulative area under the concentration-time curve over the six-months Induction ($AUC_{0\text{-}180}$) estimated using actual dosing history and individual PK parameters was used to assess (1) similarity in exposure between children and adults; (2) similarity in exposure, -B-cells response, -probability of Month 6 remission, and -probabilities of occurrence of adverse events relationships.

Finally, simulated exposure was compared between adults and pediatrics to support the extrapolation to children from 2 to < 6 years old (yo), age group not included in PePRS, and a proposal for a standardized maintenance regimen in pediatrics.

Results: A linear 2-compartment model described RTX PK. Model parameters were in the typical range for mAbs (Table 1).

In both adults and pediatrics, RTX induced a rapid and prolonged B-cell depletion across the whole range of exposure with B-cell depletion lasting longer in patients with higher exposure. Similar to adults, no association was found between variability in exposure and clinical efficacy and safety endpoints in pediatrics, suggesting the Induction regimen resulted in exposure at the plateau of the ER relationship.

Known features of FcRn and IgG biology in children, the strong relationship between RTX CL and BSA, with similar $AUC_{0\text{-}180}$ in children compared to adults across the entire range of BSA and supportive PK simulations suggested that RTX disposition in ≥ 2 to< 6 yo pts is expected to be similar to the one assessed in children ≥6 yo. In addition, simulations showed that a 250 mg/m^2 dosing regimen in children is expected to result in comparable exposure to adults treated with the approved follow-up dose of twice 500 mg administered 2 weeks apart.

Conclusion: In summary, this work supported the regulatory approval of the first pediatric indication for MabThera/Rituxan. An induction regimen of 4 weekly IV infusions of 375 mg/m^2 is recommended in children ≥2 years of age with GPA or MPA, in US and Europe. A follow-up dosing regimen consisting of two 250 mg/m^2 IV infusions separately by two weeks, followed by a 250 mg/m^2 IV infusion every 6 months, is also approved in the US.