Model-Informed Drug Approach to Recommend Therapeutic Burosumab Dosing Regimens for Pediatric and Adult Patients with Tumor-Induced Osteomalacia

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Abstract

Aim: Burosumab is approved for the treatment of X-linked hypophosphatemia (XLH) and hypophosphatemia secondary to persistent tumor-induced osteomalacia (TIO). The relationship between burosumab and fasting serum phosphate levels were previously described in patients with XLH. This work evaluated burosumab pharmacokinetic (PK) and PK/pharmacodynamic (PD) in the TIO population to support TIO dosing. Methods: Previously developed PK and PK/PD models in XLH were fitted to the combined dataset of patients with XLH and TIO to understand PK and PK/PD characteristics and covariates specific to TIO. Simulations of PK and PK/PD profiles were performed using the final models to support dosing recommendations for adult and pediatric patients with TIO. Results: Burosumab PK and PK/PD models were similar to those previously described in XLH, with additional covariates identified in TIO: baseline FGF23 on PK/PD parameters, and steeped PK/PD curve in TIO. Simulations demonstrated that in pediatric patients starting doses of burosumab 0.3 mg/kg and 0.4 mg/kg Q2W at steady state would achieve normal serum phosphate levels in at least 30% of patients with relatively low risk of hyperphosphatemia (<3% of patients), while in adults, burosumab 0.3 mg/kg and 0.5 mg/kg Q4W achieves similar percentages of responders and relative low risk of hyperphosphatemia (<7%) Titration based burosumab dosing increased the probability of achieving normal serum phosphate levels. Conclusions: This analysis identified the predictors and quantified the relationship between burosumab serum concentrations and fasting serum phosphate levels amongst patients with TIO. The models supported titration based burosumab dosing, guided by monitoring fasting serum phosphate levels.

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