Sparse sampling design for characterizing individual PK of recombinant factor VIII fusion protein (rFVIIIFc) in prophylactic treatment of Hemophilia A

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Abstract

Objectives: To determine sparse sampling times for estimating individual rFVIIIFc maximum a priori (MAP) Bayesian estimates in children ($<$12yr) and adults/adolescents ($\geq$12yr) and to evaluate the effectiveness of the recommended times to estimate individual pharmacokinetic (PK) parameters.

Methods: Fisher information matrix (FIM) for Bayesian MAP estimator [1] was implemented in PopDes, determinant of the FIM was optimized to derive optimal sampling times, assuming a dose of 50 IU/kg and 10 minutes intravenous infusion. Previously developed population PK model provided prior information. Robust three and two time points were proposed to estimate individual PK parameters based on Bayesian methodology and their effectiveness was investigated using simulations. Plasma FVIII activities of 1000 random individuals were simulated using the population PK model for different designs, individual MAP Bayesian estimates and their relative errors were determined.

Results: Optimal three sampling times for children and adolescent/adults were identified. Despite informative prior on volume, an earlier time-point at 0.5h was explored for the robust, practical sampling design to better estimate individual volume. Robust and practical three and two time points designs were identified for children and adults/adolescents with efficiencies relative to the optimal time points of approximately 91% and 83% for three and two time points respectively. Due to possible loss of information to data below lower limit of quantification at later time points, alternative three and two time points were derived; (0.5, 24, 48)h and (0.5, 48)h for children and (0.5, 48, 72)h and (0.5, 72)h for adults/adolescents. Relative to the optimal time points, the efficiencies of these designs were approximately between 70% and 95%. Simulation results showed adequate MAP Bayesian parameter estimation by both robust designs; mostly with relative errors within 25 to 30%.

Conclusion: Robust three and two sampling times for estimation of individual MAP Bayesian estimates were successfully derived and the simulations indicated that these allowed adequate estimation of individual PK of rFVIIIFc which could then subsequently be utilized for dose individualization.

References:

[1] Hennig S., Nyberg J., Fanta S, Backman J.T., Hoppu K., Hooker A.C., Karlsson M.O. Application of the optimal design approach to improve a pretransplant drug dose finding design for ciclosporin. *The Journal of Clinical Pharmacology*, 52: 347-60 (2012)