Background and Overview

- The DINAMO study was designed to evaluate the efficacy and safety of empagliflozin and linagliptin in pediatric patients with type 2 diabetes mellitus (T2DM) [4].
- Following FDA guidance for pediatric extrapolation, we leveraged previously developed PK and ER models for empagliflozin and linagliptin, built primarily on adult data, to predict treatment effects in the pediatric population.
- A Bayesian analysis was developed using a robust mixture prior [1, 2, 3]. Prior variances and a prior weight for the informative component in the mixture were pre-specified according to a previously published justification [4, 5].
- Justification for the prior mean of pediatric outcomes based on PK and ER model is explored herein and involves extrapolation from the adult population using relevant covariate adjustments (e.g., weight, eGFR, age, race, and sex).

Results

- PK models were estimated in adult and limited pediatric data with relevant covariate correction (e.g., weight, eGFR, age, race, and sex).
- The ER model for empagliflozin was based solely on adult data, whereas the model for linagliptin leveraged adult and adolescent data.
- Both ER models included relevant covariate adjustments (e.g., weight, eGFR, race, sex, and concomitant medication).
- The covariate adjustments were assumed to be sufficient to allow for pediatric extrapolation given the confidence in describing differences in exposure after allometric scaling by weight and having observed comparable responses for short-term marks of efficacy (primary glucose excursion for empagliflozin, and DPP-4 inhibition for linagliptin) in pediatric patients with T2DM relative to adults.
- The covariate adjustment strategy was also retrospectively evaluated via causal selection graphs as a formal justification for transportability between populations [6].
- Pediatric predictions adjusted for variables were represented in rectangles, while uncolored ellipses indicate variables that were likely to influence the outcome but were not adjusted for in the model. Age is a special case, since it was adjusted for in the pharmacokinetic simulations but not in the pharmacodynamic simulations. Prior evidence suggested that (conditional on eGFR) serum glucose excursion (SGE) does not depend on age, providing support for the lack of direct effect of age on change in HbA1c (Figure 2).
- The adjustment sets computed from this analysis imply that valid extrapolation is possible either by direct adjustment for age or by adjustment for body weight, eGFR, and concomitant medication (as long as the effects of age are mediated by these latter three variables, as implied by Figure 2).

Conclusion

- Bayesian borrowing is an increasingly popular technique for evidence integration [7].
- Bayesian borrowing can be informed by prior beliefs about conditional exchangeability (the idea that certain observations are comparable after making known covariate adjustment) while also providing a fail-safe if these exchangeability assumptions become inconsistent with the data.
- The acceptance of the results also relies upon the pre-specification of the prior weight and the assessment of subsequent sensitivity analyses [7,8].
- Collaboration between pharmacometricians, statisticians, and stakeholders about the proposed methodology early on, prior to model development, can increase confidence and support successful implementation of Bayesian borrowing.

References


QR code