Background

Limited information is available on the factors that impact clinically on the pharmacokinetics of monoclonal antibodies (mAbs). This study was designed to identify covariates that have a significant influence on the variability of pharmacokinetic (PK) parameters of mAbs in population pharmacokinetic (POPPK) studies. Since physiologically based pharmacokinetic (PBPK) models generally offer many advantages in modelling PK of drugs, this study also investigated whether current human PBPK models account for the PK variability due to the significant covariates.

Methods

POPPK studies on mAbs were evaluated to identify covariates tested and those that had a significant impact on the PK variability of the mAbs. These covariates were also ranked in order of the number of POPPK studies that identified them as significant covariates. Published human PBPK models for mAbs were evaluated for their potential ability to account for variability in PK, with special reference to the significant covariates identified by POPPK studies.

Results

Evaluation of 37 POPPK studies showed that 59 different covariates were tested and 17 were identified as significant covariates, as shown in Figure 1. Figure 2 and Figure 3 depict the relevance of the significant covariates with reference to the total number of POPPK studies reviewed and the number of studies that tested the covariates.

Ten human PBPK models were reviewed. It was evident that this research area is rapidly developing with the focus on optimally predicting clinical observations based on the complex mechanistic principles governing mAb disposition. None of the current PBPK models have accounted for population variability due to the covariates in Figure 1, although models linked to population databases may have the potential to account for relevant covariates, including demographics, target concentration, and route and dose.

Conclusion

Weight, dose and antibodies appear to be important variables in mAb PK. Formulation and route of administration showed significance in the single study in which they were tested. Since current PBPK models do not account for population variability due to relevant covariates, future models may benefit from considering them.

References

1. Li et al., 2014, AAPS J Sept; 16(5):1097-1109