EMERGING COVARIATES ON THE PHARMACOKINETICS OF MONOCLONAL ANTIBODIES: DO CURRENT PBPK MODELS ACCOUNT FOR THE SIGNIFICANT COVARIATES IDENTIFIED IN POPPK STUDIES?

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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.

1 age
2 antibodies
3 aspartate aminotransferase
4 body surface area
5 concurrent medication
6 creatinine clearance
7 C-reactive protein
8 Dose
9 ethnicity
10 formulation
11 route
12 serum albumin
13 sex
14 smoking
15 target protein concentration
16 White Blood Cells
17 weight
18 body mass index
19 diagnosis
20 height
21 bilirubin
22 alanine aminotransferase
23 disease stage
24 endogenous IgG
25 disease sites
26 tumour type
27 tumour burden
28 number of metastatic sites
29 ideal body weight
30 blood urea nitrogen
32 serum creatinine
33 treatment duration
34 SGOT
35 alanine phosphatase
36 total cholesterol
37 high density lipoprotein
38 low density lipoprotein
39 total protein
40 direct bilirubin
41 indirect bilirubin
42 comorbidities
43 prior doses
44 baseline drug concentration
45 disease duration
46 alcohol use
47 nonsteroidal anti-inflammatory use
48 lactate dehydrogenase
49 study site
50 Karnofsky index
51 study number
52 concurrent chemotherapy
53 free fat mass
54 lymphocyte count
55 baseline steroid use
56 baseline gene signature
57 lean body mass
58 transporter genotypes
59 CYP enzyme genotypes

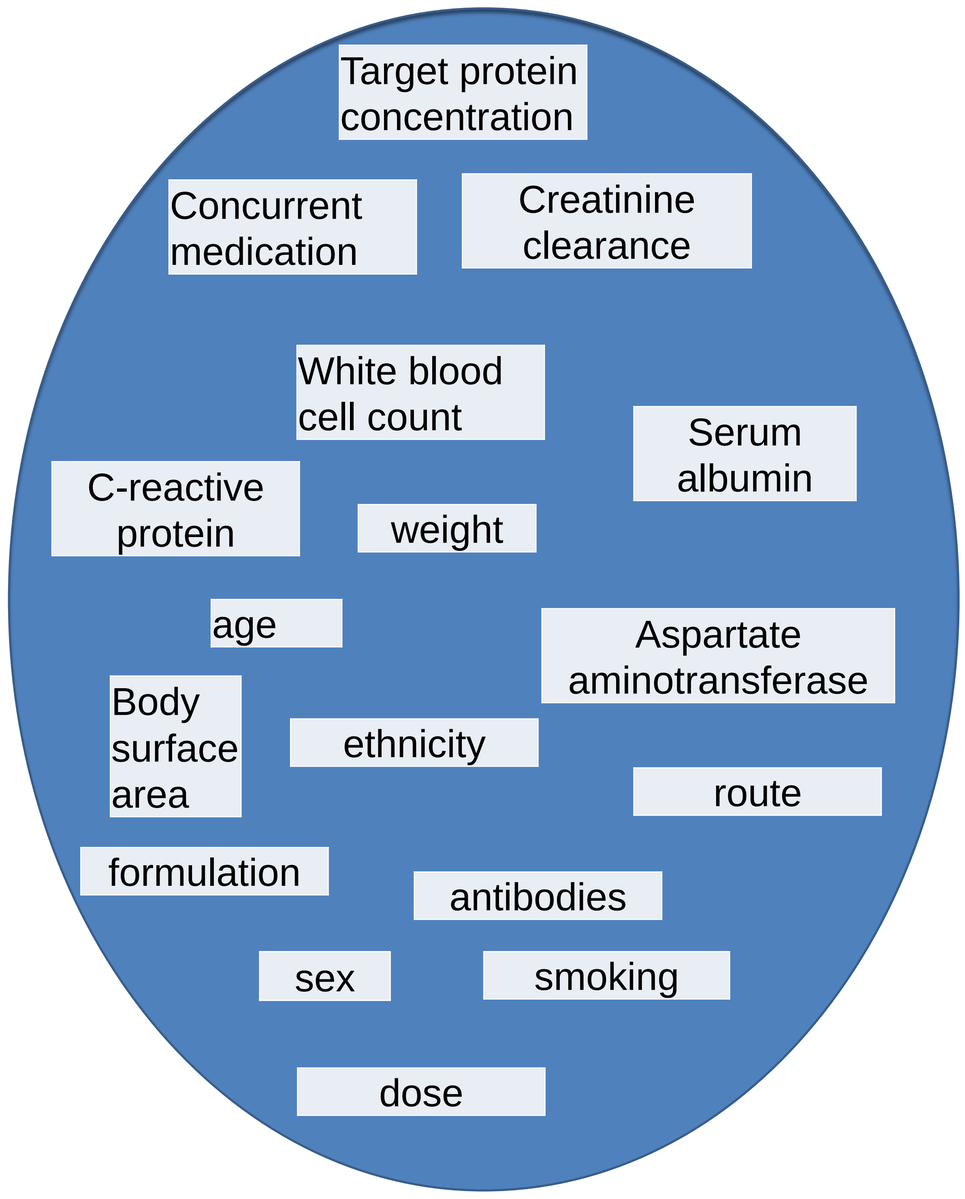

Figure 1: Covariates tested are shown in the green block and significant covariates can be seen in the blue oval.

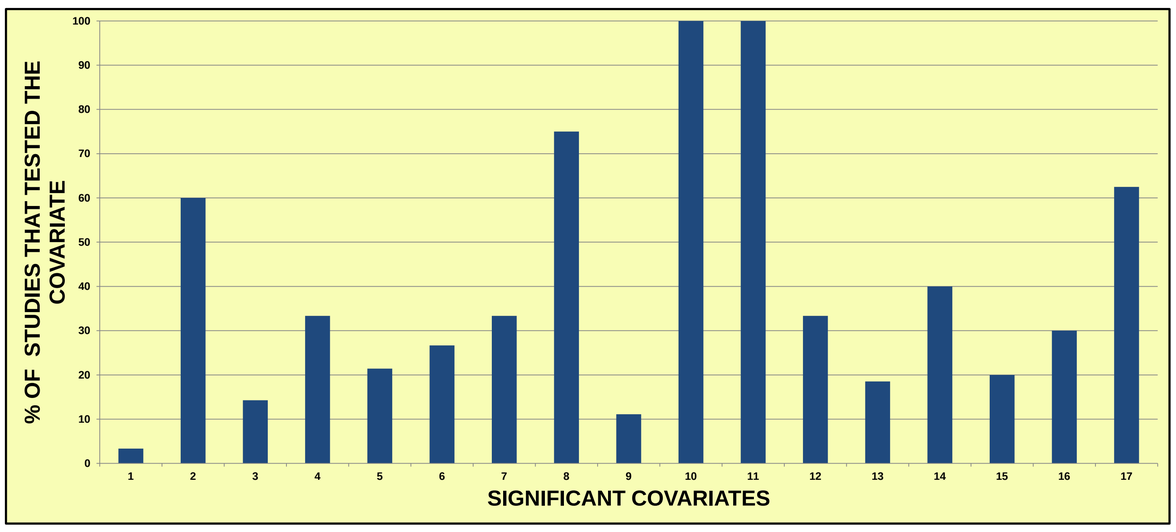

Figure 2: Significance of the covariates relative to the number of POPPK studies that tested them
Note: covariate numbers correspond to those in Figure 1

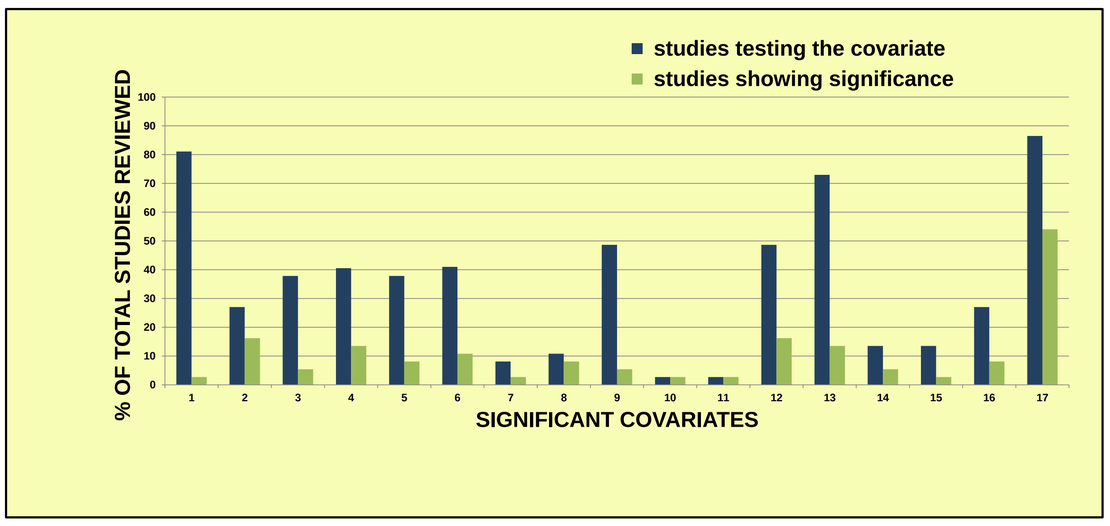

Figure 3: Significance of the covariates relative to total number of POPPK studies reviewed.
Note: covariate numbers correspond to those in Figure 1

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[1] may have the potential to account for relevant covariates, including demographics, target concentration, 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