Exploring fixed dose versus body weight based dosing for monoclonal antibodies using physiologically based pharmacokinetic modelling.

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Purpose

Although a fixed dosing regimen is simpler to administer, reduces the risk of medication errors, favours compliance and is generally more cost-effective, some monoclonal antibodies (mAbs) may benefit from body weight based dosing. By using body weight based dosing, it is assumed that inter-individual variability in exposure to the drug is minimized. A recent study has shown that fixed dosing is better for some mAbs while weight based dosing reduces variability in exposure for others mAbs.[1] The aim of this study was to determine whether physiologically based pharmacokinetic (PBPK) models, which incorporate inter-individual variability in systems parameters, are effective in predicting the more appropriate dosing strategy for mAbs.

Method

The Simcyp Population Based Simulator (V13 R1) was used to simulate concentration-time profiles for omalizumab (150mg and 300mg) and efalizumab (1mg/kg and 10mg/kg) using study designs that were as close as possible to the published clinical studies.[2,3] A minimal PBPK model with TMDD was used for both mAbs. A full TMDD model was used for omalizumab while a Michaelis-Menten approximation[4] was applied to efalizumab. Suitability of the models was verified by comparing the predicted pharmacokinetic (PK) profiles with those observed clinically.

Using these models and 500 virtual healthy volunteers, PK profiles were simulated for each mAb using the following single doses:

Omalizumab – 150mg, 2mg/kg, 300mg and 4mg/kg

Efalizumab - 75mg, 1mg/kg, 750mg and 10mg/kg.

The study population was stratified into the following groups based on weight as follows: 40 – 50 kg; 51-60 kg; 61-70kg; 71-80kg; 81-90 kg; 91-100 kg; 101-110kg; ≥111kg.

The means of the area under the plasma concentration versus time curve (AUC_{0-t}) and maximum plasma concentration (Cmax) for each weight group were compared for variability with the fixed dose versus weight based dosing options. Variability was also evaluated by the fold difference between the lowest and highest value for each of the above PK parameters, using the mean of the predicted values for the different weight groups. A difference of >2 fold was considered to be significant.

Results

Visual inspection of the predicted concentration versus time profiles for the mAbs compared with clinically observed data suggested that the selected models successfully recovered the clinical data, as shown in Figure 1.

A comparison of AUC_{0-t} and Cmax resulting from the two dosing approaches in different weight groups is shown in Figure 2. Variability in Cmax between different weight groups is minimized for efalizumab when it is dosed based on weight.

Variability ratios for AUC_{0-t} and Cmax following the different dosing approaches are tabulated in Table 1. Significant variability is observed when efalizumab is given in fixed doses.

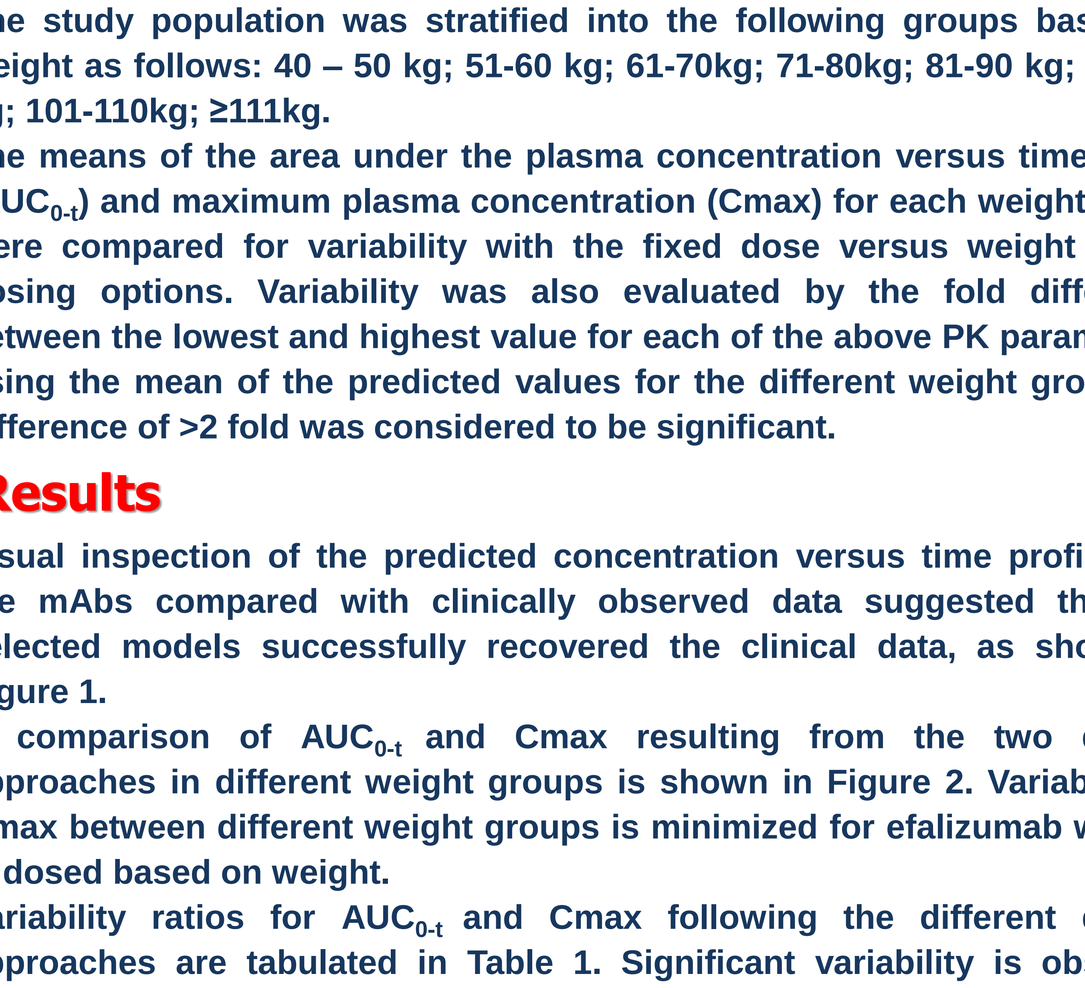

Figure 1: Predicted and observed concentration versus time profiles for two doses of omalizumab and efalizumab.

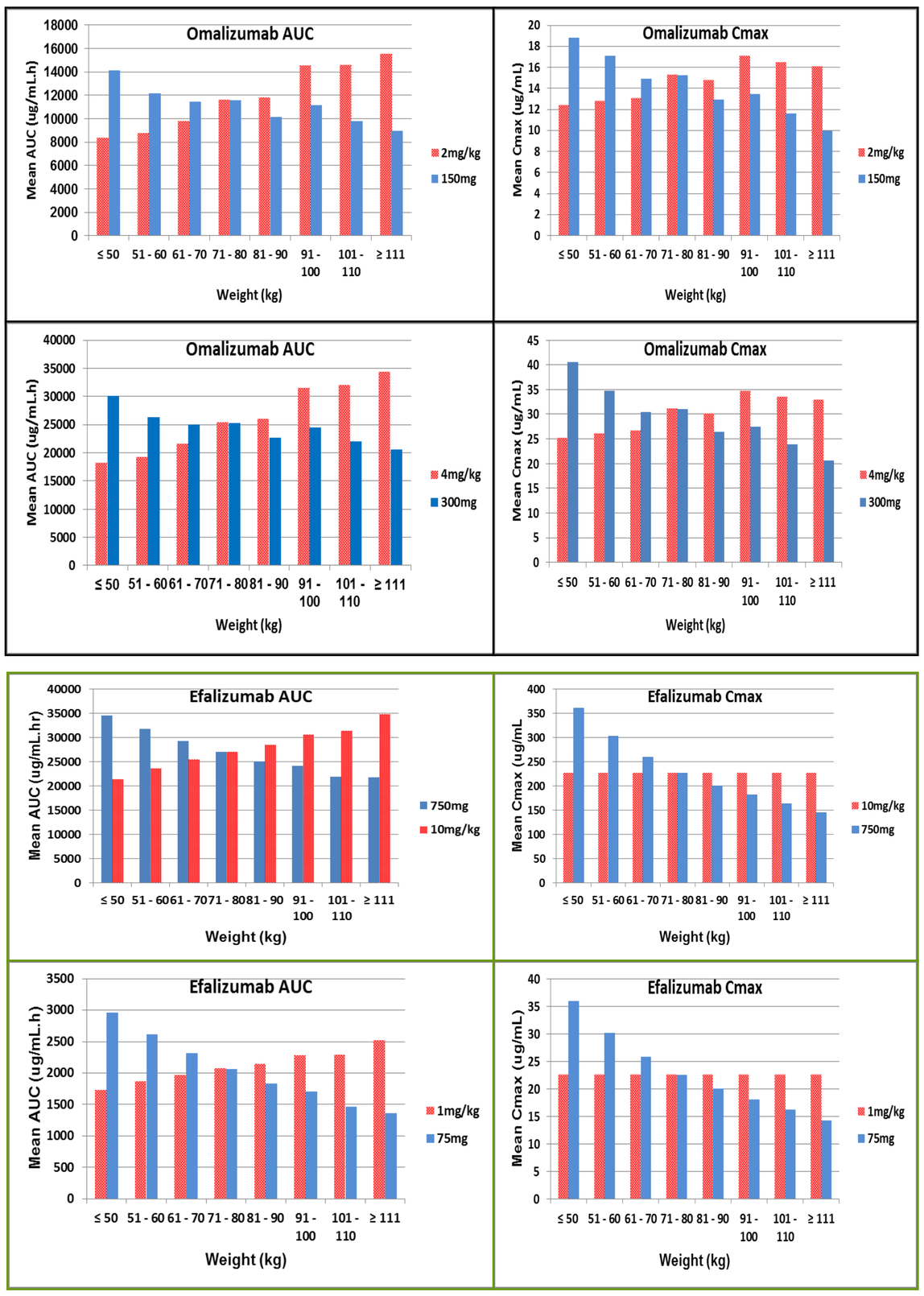

Figure 2: Comparison of predicted AUC and Cmax for fixed dose and weight based dosing of omalizumab and efalizumab.

Table 1: Variability ratios for AUC and Cmax following different dosing approaches for omalizumab and efalizumab.

Efalizumab dose	AUC ratio	Cmax ratio	Omalizumab dose	AUC ratio	Cmax ratio
1mg/kg	1.46	1	2mg/kg	1.86	1.38
75 mg	2.18	2.52	150 mg	1.58	1.88
10mg/kg	1.63	1	4mg/kg	1.89	1.30
750 mg	1.79	2.49	300 mg	1.46	1.96

Conclusion

Variability in AUC and Cmax was observed between the weight groups with both the two dosing approaches for omalizumab. The fold differences in AUC (>2 fold) and Cmax (>2 fold) suggest that weight based dosing is more appropriate for efalizumab. Decisions on dosing for omalizumab may require further investigation since there is no clear advantage of one approach over the other. These predictions are inline with dosing recommendations for these mAbs, where weight based dosing had been used for efalizumab while omalizumab dosing is based on an algorithm with mg/kg and IgE level.

This preliminary study suggests that simulations using PBPK modelling can be useful in predicting the suitability of dosing options for mAbs.

References

1. Wang et al. J Clin Pharmac, 2009, 49:1012-1024
2. Bauer et al. J Pharmacokinet Biopharm, 1999, 27: 397-420
3. Riviere et al. J Bioequiv Availab, 2011, 3(6):144-50
4. Gibiansky et al. J Pharmacokinet Pharmacodyn, DOI 10.1007/s10928-008-9102-8