Prediction of mAb disposition in hepatic impairment – Evolocumab as a case study

Kate Gill & Iain Gardner

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

Abstract

An increase in the transcapillary escape rate of IgG has been reported in hepatic impairment (HI) patients (Henriksen *et al.*, 1980). This is anticipated to also result in increased convective flow of mAbs in HI patients leading to decreased plasma concentrations. PBPK modelling was used to incorporate the change in convective flow and hence predict the impact of HI on evolocumab plasma concentrations. The model was able to capture the extent of the decrease in systemic exposure, with predicted and observed AUC ratios (HI/Healthy subjects) of 0.59 and 0.57, respectively. Further work is required to validate this further for HI and other disease states.

Background

Hepatic impairment (HI) is not thought to have a significant impact on mAb pharmacokinetics, unlike its effects on many small molecule drugs. However, the transcapillary escape rate (TER) of albumin and IgG is increased in several disease states, including HI (Malik *et al.*, 2017; Henriksen *et al.*, 1980). Increased extravasation of proteins in HI is anticipated to result in increased distribution and decreased plasma concentrations. This theory was tested using a PBPK modelling approach to describe Evolocumab disposition in healthy and HI subjects.

Methods

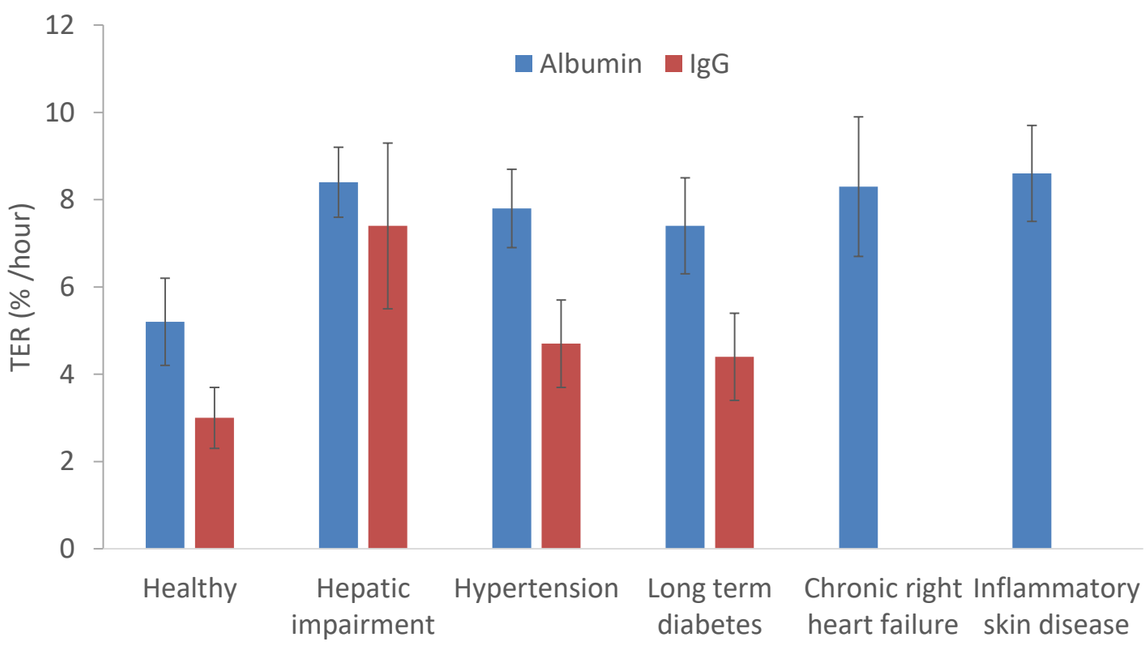
TER data for albumin and IgG in healthy and diseased subjects were extracted from the literature (Malik *et al.*, 2017; Henriksen *et al.*, 1980). The fold change in IgG TER between healthy volunteers and HI was calculated.

A PBPK model was developed for Evolocumab using the minimal PBPK model for mAbs in Simcyp V18R2. K_{D1}, K_{up}, K_{rc1}, σ_v, σ_l, FR and CL_{cat} were all assumed to be the same as endogenous IgG as no evolocumab specific data for these parameters could be found in the literature. Additional systemic clearance, fa and ka were fitted to the healthy volunteer concentration data from Gibbs *et al.*, 2017. The Sim-Healthy Volunteer population was used and the trial design was matched to the published study. 10 trials of 8 subjects were simulated.

For simulations of Evolocumab disposition in HI patients, the Sim-Cirrhosis CP-B population was used. σ_v represents the restriction to convective movement of mAbs from the blood to the interstitial space. 1-σ_v for endogenous IgG and Evolocumab was increased by 2.47-fold reflecting the extent of the increase in TER for IgG in HI subjects. Endogenous IgG concentrations were also increased in the Sim-Cirrhosis CP-B population by the same extent (1.45-fold) as the reported increase in CP-B HI subjects (Gibbs *et al.*, 2017). All other parameter values remained the same. Simulations were performed using matched study designs to the in vivo study. 10 trials of 8 subjects were simulated.

Results

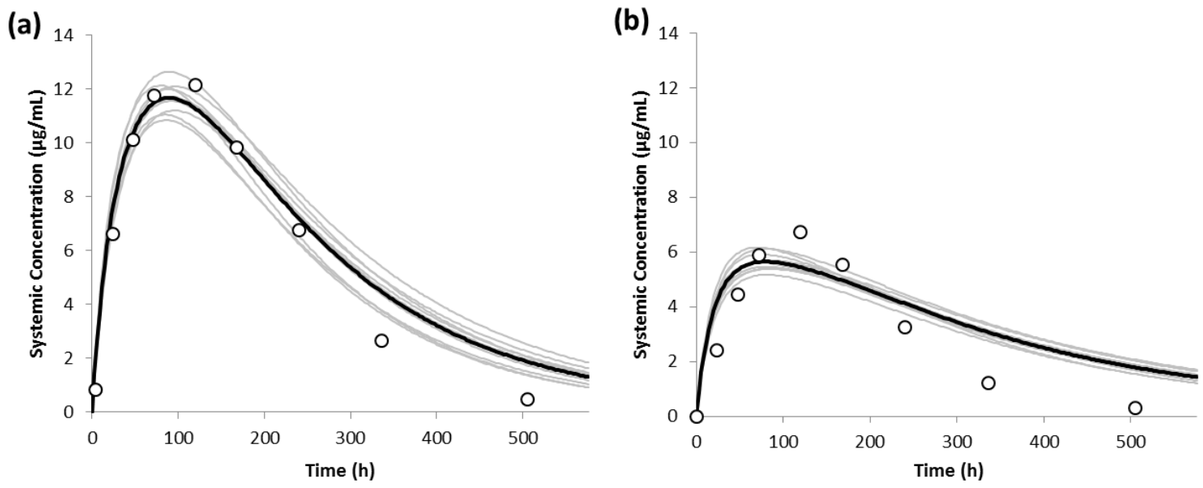
Figure 1: Transcapillary escape rate of albumin and IgG in healthy and diseased subjects



TER for albumin and IgG in healthy and diseased subjects were extracted from the literature (Malik *et al.*, 2017; Henriksen *et al.*, 1980) and are presented in Figure 1. TER for IgG was 2.47-fold higher in HI patients compared to healthy subjects.

The PBPK model for evolocumab was developed in a healthy volunteer population (Figure 2a).

Figure 2: Observed (circles = Gibbs *et al.*, 2017) and predicted (bold line = population mean; grey lines = trial means) plasma concentration-time profiles for evolocumab in healthy (a) and HI (b) subjects



Plasma concentrations of evolocumab are reduced in HI but clearance by TMDD remains the same as in healthy volunteers (Gibbs *et a*l., 2017). By accounting for the increased extravasation of proteins in HI in the PBPK model the reduction in exposure to evolocumab was predicted reasonably well (Figure 2b). Predicted AUC values were within 50% of observed values (Table 1). The observed AUC ratio for HI/healthy subjects was also captured by the model (Table 1).

Table 1: Observed and predicted geometric mean AUC for evolocumab

	AUC0-∞ (µg.hr/mL)		AUC ratio (Healthy/HI)
	Healthy	HI	
Observed	2568	1454	0.57
Predicted	3317	1964	0.59
Predicted/observed	1.29	1.35	1.04

Conclusions

- Extravasation of proteins is increased in HI, which was theorised to lead to an increase in mAb distribution and decrease in systemic exposure.
- A PBPK model was developed for evolocumab in healthy subjects.
- By accounting for the increased extravasation of IgG in HI subjects the observed reduction in systemic exposure could be predicted by the PBPK model.
- Further validation with clinical data for other mAbs in healthy and HI subjects is required, however, suitable data are scarce in the literature.
- The PBPK model framework detailed here could be used to explore the impact of increased extravasation of proteins in other disease states. Reduced systemic exposure of mAbs in such subjects is expected, although the extent may vary compared to HI patients.
- Increased distribution of mAbs in disease will result in higher tissue exposure and could lead to increased efficacy and/or toxicity (Malik *et al.*, 2017).

References

- Gibbs *et al.*, J Clin Pharmacol (2017), 57(4): 513–523.
- Malik *et al.*, J Pharmacokinet Pharmacodyn (2017) 44:277–290.
- Henriksen *et al.*, Scand J Clin Lab Invest (1980) 40: 121-128.

20th Annual Simcyp Consortium Meeting, Sheffield, UK, 17-19th September 2019