

Physiologically-based pharmacokinetic modelling to predict antibody exposure in hepatic impairment

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Background and Objective

- Hepatic impairment (HI) is a common comorbidity in cancer patients [1].
- HI could have an impact on the PK of monoclonal antibodies (mAbs) and antibody-drug conjugates.
- Alirocumab and evolocumab are two PCSK9 antagonists, which have a dedicated clinical study in patients with mild and moderate HI [2, 3].
- IgG concentration can be increased in patients with HI [4]. Higher IgG levels could explain the decreased mAb exposure, observed for alicrocumab and evolocumab in HI patients [2, 3].
- A physiologically-based pharmacokinetic (PBPK) model was used to evaluate the changes in IgG concentration on the PK of alicrocumab and evolocumab.

Methods

- A whole-body PBPK model for biologics, implemented in the Simcyp Simulator V24[®], was used [5].
- Literature search was conducted to find IgG serum concentration in patients with HI.
- Alirocumab and evolocumab were used to evaluate the model performance (Table 1).
- The measured PCSK9 concentration were used to consider the effect of HI on the antibody target (Table 2).

Results

- Serum IgG levels in liver cirrhosis were reported in six studies, ranging from 8.6 to 40 g/L (value in healthy controls: ~12 g/L).
- The fold increase of IgG concentration compared with healthy controls was 1.4, 1.5, and 2.0 in mild, moderate, and severe HI.
- Clinically observed concentration-time profiles of both investigated mAbs were predicted in accordance with the clinically observed data for healthy controls and patients with mild and moderate HI, classified by the Child-Pugh score (Figure 1-3).
- PK parameters were generally predicted within 1.5-fold of the observed data, except for the AUC of evolocumab, which was predicted within 1.7-fold.
- Predictions of alicrocumab did not improve with the elevated IgG levels, obtained from the literature (predicted:observed ratios were all within 1.5-fold; Table 3).
- Predictions of evolocumab improved by considering the elevated IgG levels in mild and moderate HI (predicted:observed ratios were all within 1.25-fold; Table 4).

Conclusion

- The PBPK approach can be successfully used to simulate the PK of mAbs in HI.
- IgG has high variability in HI, and some patients might have elevated IgG levels that impact the PK as shown for evolocumab.
- Sensitivity analysis is recommended with baseline IgG, mean elevated IgG, and the maximum IgG concentration to predict the worst-case scenario.

Table 1: Input parameters for the two investigated antibodies.

	Alirocumab	Evolocumab
Absorption Model	Mechanistic SC model	Mechanistic SC model
Distribution Model	Full PBPK	Full PBPK
KD to FcRn (μM)	0.728	Assume IgG default 0.728
Cladd (L/h)	0	0.0073
KD to PCSK9 (μM)	0.00019	[6] 0.0016
Kint (1/h)	0.0031	[2] 0.0031

SC = subcutaneous, Cladd = additional systemic clearance, Kint = internalization rate.

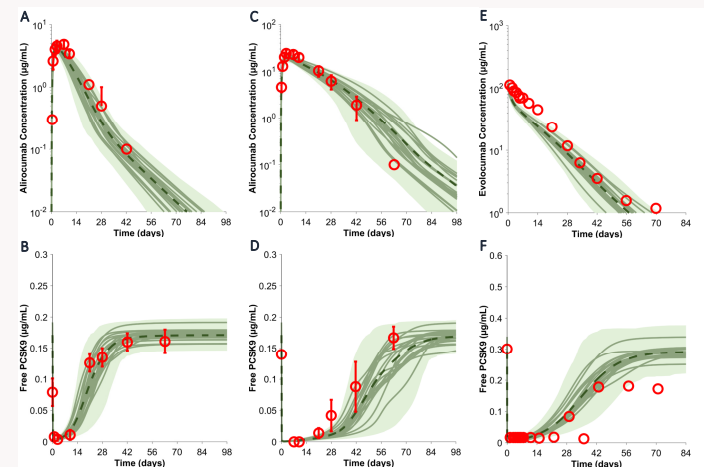


Figure 1: Predicted vs. observed plasma concentration for alicrocumab (A: 50mg, C: 250 mg), evolocumab (E: 420 mg) and the free target (B, D, F) in healthy controls. Red markers show the observed data. The dashed line and the shaded area are the mean and 95% CI of the simulated population, and the solid lines are the mean of each virtual trial.

Table 2: PCSK9 target abundance (Rmax) in controls, Child-Pugh A (CP-A), and Child-Pugh B (CP-B) patients.

Rmax (μM)	Control	CP-A	CP-B
Alirocumab	0.00447	0.00542	0.00476
Evolocumab	0.00286	0.00253	0.0022

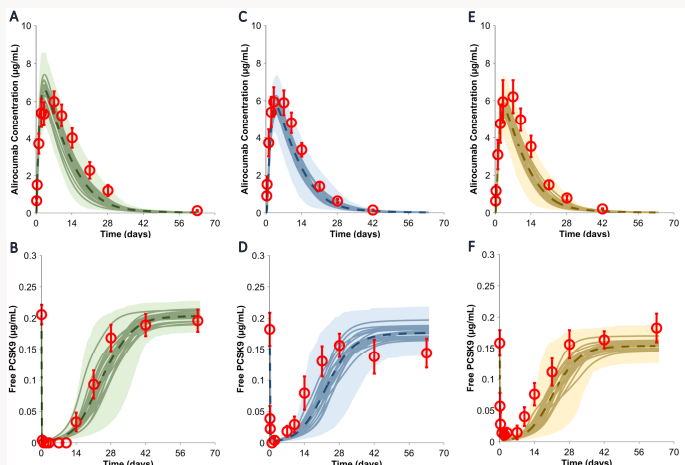


Figure 2: Predicted vs. observed plasma concentration for alicrocumab (75 mg) and the free target in healthy controls (A, B), mild HI (C, D), and moderate HI (E, F). Red markers show the observed data. The solid lines, dashed line and the shaded area are the mean of each trial and mean and 95% CI of the simulated population.

Table 3: Predicted vs. observed ratio disease/healthy with and without elevated IgG levels for alicrocumab.

	Alirocumab					
	observed		predicted		predicted – IgG ↑	
	CP-A/Con	CP-B/Con	CP-A/Con	CP-B/Con	CP-A/Con	CP-B/Con
Cmax	0.96	1.00	0.84	0.86	0.78	0.74
AUC _{inf}	0.83	0.80	0.78	0.84	0.61	0.53

Con = Controls, CP-A = Child-Pugh A, CP-B = Child-Pugh B.

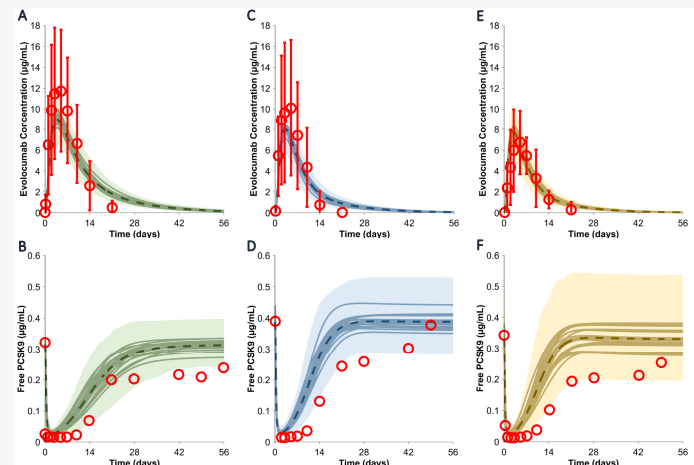


Figure 3: Predicted vs. observed plasma concentration for evolocumab (140 mg) and the free target in healthy controls (A, B), mild HI (C, D), and moderate HI (E, F). Red markers show the observed data. The solid lines, dashed line and the shaded area are the mean of each trial and mean and 95% CI of the simulated population.

Table 4: Predicted vs. observed ratio disease/healthy with and without elevated IgG levels for evolocumab.

	Evolocumab					
	observed		predicted		predicted – IgG ↑	
	CP-A/Con	CP-B/Con	CP-A/Con	CP-B/Con	CP-A/Con	CP-B/Con
Cmax	0.78	0.66	0.96	0.94	0.89	0.86
AUC _{inf}	0.79	0.57	0.85	0.83	0.66	0.60

Con = Controls, CP-A = Child-Pugh A, CP-B = Child-Pugh B.

References

- [1] Krens et al. The Lancet Oncology 2019, 20, e200-7.
- [2] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000ClinPharm.pdf.
- [3] Gibbs et al. J Clin Pharmacol 2017, 57, 513-23.
- [4] Sun et al., Clin Pharmacol Ther 2020, 107, 1256-62.
- [5] Huang et al. Front Pharmacol 2022, 13, 974423.
- [6] Shen et al. PLoS One 2017, 12, e0183326.
- [7] https://www.ema.europa.eu/en/documents/assessment-report/repatha-epar-public-assessment-report_en.pdf



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