Modelling the effect of interleukin-6, an inflammatory cytokine, on time-dependent reduction of cyclosporine clearance : An application of the Simcyp Population-based Simulator to suppression of CYP450 by biologics

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Introduction

Biologics/therapeutic proteins (TPs) such as cytokines or modulators of cytokines, can differentially influence the expression and stability of specific CYP450 enzymes[1,2,3] (Fig. 1) with consequences for clearance of other drugs which are dependent on these enzymes for their elimination.

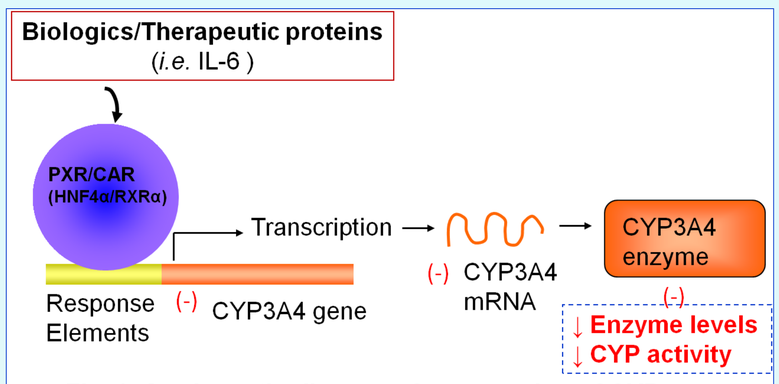

Fig. 1: A schematic diagram of suppression of CYPs by Biologics in Liver

It has been reported that the cytokine, interleukin-6 (IL-6), down-regulates CYP3A4 mRNA by 90% *in vitro* in human hepatocytes[2]. A clinical study[4] in subjects receiving cyclosporine following a bone marrow transplant (BMT) reported increased exposure to the CYP3A substrate, cyclosporine, supporting the hypothesis that CYP3A is modulated by this cytokine. This has implications for the drug treatment of patients with inflammatory diseases that experience elevated IL-6 levels[3] and also for patients receiving anti-IL-6 receptor antagonists[5] .

Although there are emerging experimental data[2,5] that characterize the effects of TPs on CYP enzymes *in vitro*, interpretation of these data in terms of predicting the magnitude of DDIs *in vivo* remains unclear.

Objectives

To use prior *in vitro* information unfolding the decrease in CYP3A mRNA and Physiological-Based Pharmacokinetic (PBPK) modeling in conjunction with clinical data describing IL-6 exposure in BMT patients to predict the magnitude of DDI with cyclosporine using the Simcyp Simulator (Version 10.1).

Methods

A minimal PBPK model with a semi-mechanistic link model involving suppression of CYP3A4 was used in the present study. The effect of IL-6 was investigated on the cyclosporine PK following intravenous administration in virtual patients. The study design is consistent with that of clinical study[4].

1. Fitting systemic IL-6 profiles

The changes in serum IL-6 levels from two representative patients (Patient 1 and 5) from the clinical study[4] were fitted using appropriate PK models. The model mimicking the changes in serum IL-6 levels during inflammation in patients was analogous to using a zero order input rate (similar to i.v. infusion) and first-order elimination (eq. 1 and eq. 2).

During perturbed synthesis of IL-6:

$$\Delta(IL6) = \frac{R1 - R0}{CL}\left(1 - e^{-\frac{CL}{V}T}\right)\left(e^{-\frac{CL}{V}(t-T)}\right) \quad \text{eq.1}$$

Following perturbation to synthesis of IL-6:

$$\Delta(IL6) = \frac{R1 - R0}{CL}\left(1 - e^{-\frac{CL}{V}t}\right) \quad \text{eq. 2}$$

R0 is baseline endogenous synthesis rate of IL-6; R1 is increase in synthesis rate of IL-6 during inflammation; 't' is time from the start of the perturbation; 'T' is the duration of perturbation, CL and V where clearance and volume of distribution of IL-6, defined relative to the rate of synthesis.

2. Minimal PBPK model (Simcyp Version 10.1)

The parameters obtained from eq.1 and eq.2 were used to redefine the IL-6 within Simcyp Simulator. The Minimal PBPK option (Fig. 2) was used to define the concentration time profiles for cyclosporine and IL-6.

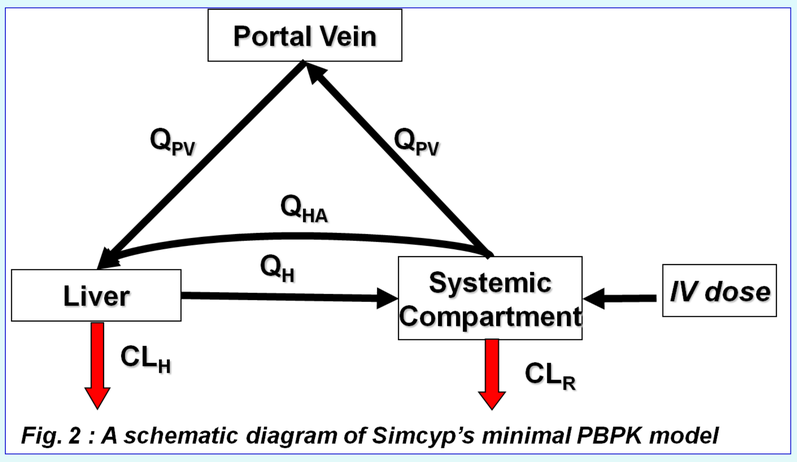

Fig. 2 : A schematic diagram of Simcyp's minimal PBPK model

Where Q_{PV} and Q_{HA} are the blood flows in the portal vein and hepatic artery, respectively; CL_H and CL_R are the hepatic and renal clearances of cyclosporine, respectively.

3. Semi-mechanistic suppression model

The *in vitro* suppression data[2] for CYP3A4 enzyme (i.e. folds of suppression; Ind_{max} = 0.1) for IL-6 was used in the turn-over model to recover inhibitory impact of time-variant concentrations of IL-6 on CYP3A4 enzyme levels in the liver (eq. 3). The semi-mechanistic suppression model within Simcyp Simulator (Version 10.1) assumes that the time-dependent concentrations of IL-6 affect the rate of enzyme synthesis directly.

$$\frac{dE_t}{dt} = k_{deg} \times E_0 \times \left(1 + \frac{(Ind_{max} - 1) \times [I]_t}{IndC_{50} + [I]_t}\right) - k_{deg} \times E_t \quad \text{eq. 3}$$

Ind_{max} is the maximum fold difference in the CYP enzyme activity relative to vehicle control (expressed as < 1); k_{deg} is the degradation rate constant for CYP enzyme (1/time); E_0 is the CYP450 enzyme level at time, 0; $IndC_{50}$ is the concentration that produces half-maximum fold suppression and E_t is the CYP450 enzyme level at time, t.

Results & Discussion

A zero order input rate and first order elimination adequately recovered the clinically reported endogenous IL-6 profiles in both patients (Fig. 3 & 4).

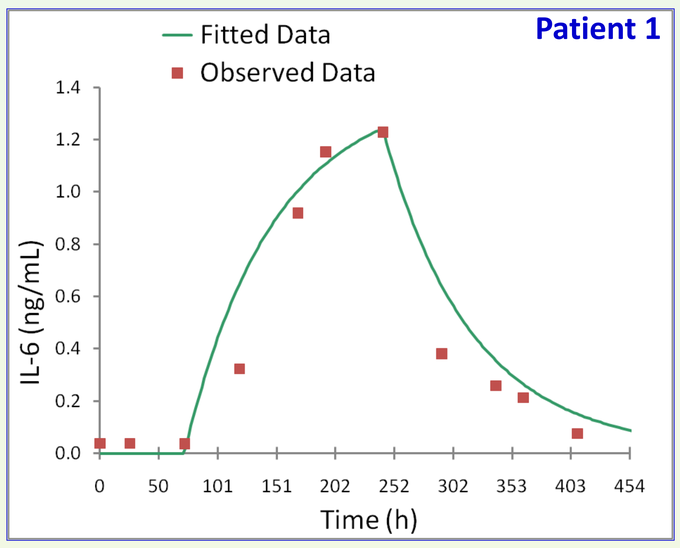

Fig. 3: Systemic concentration-time profiles for IL-6 in Patient 1 (Fitted vs. Observed)

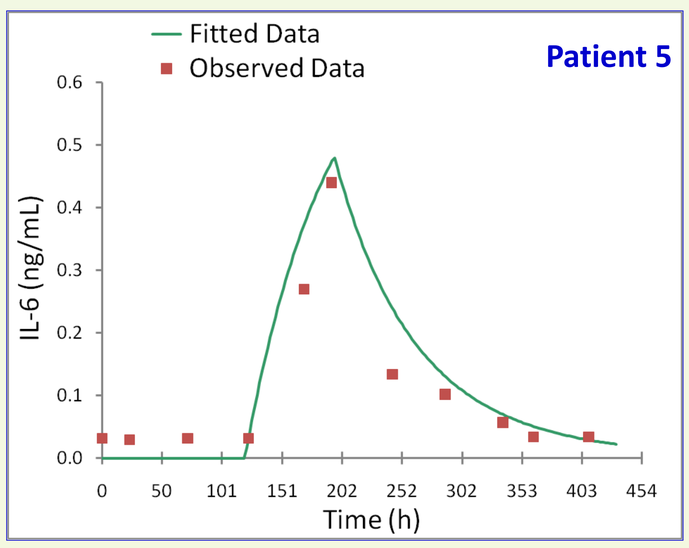

Fig. 4: Systemic concentration-time profiles for IL-6 in Patient 5 (Fitted vs. Observed)

The IVIVE-generated pattern in time-varying systemic cyclosporine levels (Fig. 5 & 6) was broadly comparable with the observed data[4].

In both patients, the peak plasma concentrations are reasonably comparable (Observed (1197-1474 ng/mL) *vs.* Predicted (1140-1224 ng/mL) (Fig. 5 & 6).

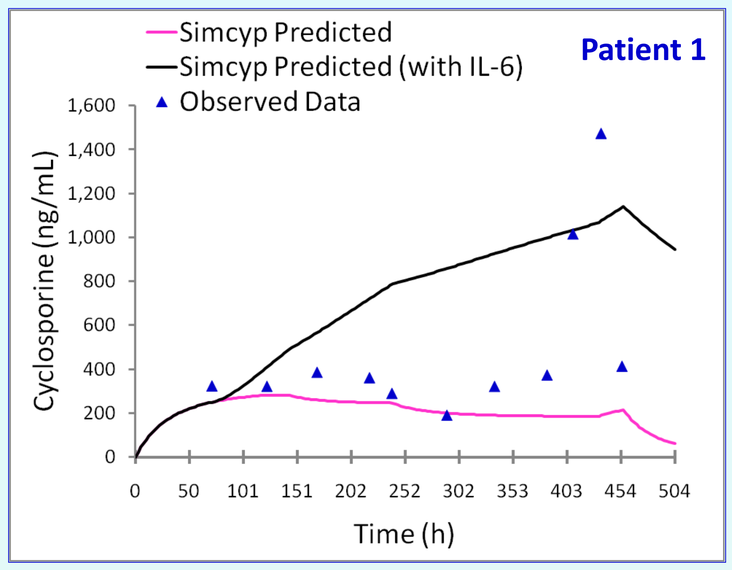

Fig 5: Systemic concentration-time profiles for cyclosporine profiles in Patient 1 (Predicted vs. Observed)

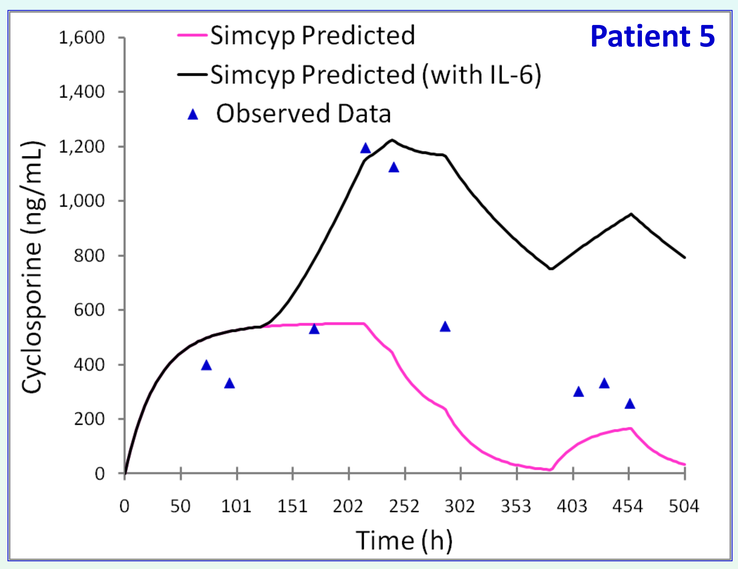

Fig 6: Systemic concentration-time profiles for cyclosporine profiles in Patient 5 (Predicted vs. Observed)

Consistent with the observed data, the linked minimal PBPK model predicted a 2-5 fold increase (i.e. relative to day 2[6]) in systemic cyclosporine levels in the presence of IL-6, compared to a 2-7 folds increase in the clinical study[4].

This suggests a clear correlation between elevated IL-6 levels and decrease in cyclosporine clearance in BMT patients, possibly *via* suppression of CYP3A4 by IL-6, consistent with the reported *in vitro* data (*i.e.* down-regulation of 90% CYP3A4 mRNA by IL-6 in human hepatocytes[2]).

The observed high inter-individual variability in IL-6 profiles in patients (Fig. 3 & 4) as well as possible involvement of other factors (*i.e.* variable levels of C-reactive protein, α1-acid glycoprotein and cyclosporine metabolites) on the magnitude of prediction was not considered in the current model.

Conclusions

Application of a novel DDI module within Simcyp Simulator was successful in demonstrating predictability of the effect of IL-6 on cyclosporine PK in patients with elevated levels of IL-6. These simulations pave the way for extrapolating the *in vitro* information on drug-drug interactions involving biologics when they are operated by suppression of CYP enzymes.

References

1. Huang SM *et al.*, (2010). *Clin Pharmacol Ther* 87:497-503.
2. Aitken AE and Morgan ET (2007). *Drug Metab Dispos* 35: 1687-1693.
3. Morgan ET *et al.*, (2008) *Drug Metab Dispos* 36: 205-216
4. Chen YL *et al.*, (1994). *Clin Pharmacol Ther* 55: 649-660
5. Zhang X *et al.*, (2009) *Clin Pharmacol Ther* 85: S59.
6. Gupta SK *et al.*, (1987). *Br J Clin Pharmacol* 24: 519-526