

Model-based dose selection of tocilizumab for the prevention of reperfusion injury

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Introduction

Whereas moderate C-reactive protein (CRP) elevation in the general population is linked to long-term risk of coronary heart disease, an exponential, acute escalation of CRP following myocardial infarction (MI) has been found to be associated with increased risk of death and cardiac complications^[1].

The inflammatory cytokine interleukin-6 (IL-6) has been shown to directly stimulate CRP expression. We hypothesise that tocilizumab (TCZ), a humanised anti-IL-6 receptor antibody which inhibits IL-6 binding to membrane-expressed IL-6R and soluble IL-6R (sIL-6R), may be useful for the treatment of reperfusion injury., which is associated with clinical procedures after myocardial infarction.

Here we explore the dose rationale for the suppression of CRP levels in patients eligible for PCA.. The ultimate objective of this investigation is to identify which dose(s) of TCZ produce a clinically significant reduction in CRP levels within 48 – 72 h after administration of the antibody.

Subjects and Methods

The evaluation of the effects of tocilizumab on CRP was used as biomarker for the anticipated clinical benefit (i.e., reduction in tissue damage due to reperfusion injury).

A model-based approach was implemented in which a virtual cohort of patients was exposed to a range of doses of tocilizumab. The patient population was created using the database from the National Health and Nutrition Examination Survey (NHANES) website, which includes demographic attributes that can be subsequently incorporated into the pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PKPD) analysis.

The starting-dose selection for our study was based on a previous research by Levi et al^[2] where TCZ was administered at doses of 4mg/kg via intravenous infusion. An existing PK model^[3] enabled the simulation of plasma concentrations, which were used as input into a pharmacokinetic-pharmacodynamic (PKPD) model describing the inhibitory effects of TCZ on CRP levels. Clinical trial simulations were then performed to characterise the overall response to the different doses.

Pharmacokinetic (PK) Analysis

The PK model describing TCZ serum concentrations is a two compartment model with parallel first-order and Michaelis-Menten (M-M) eliminations (Figure 1).

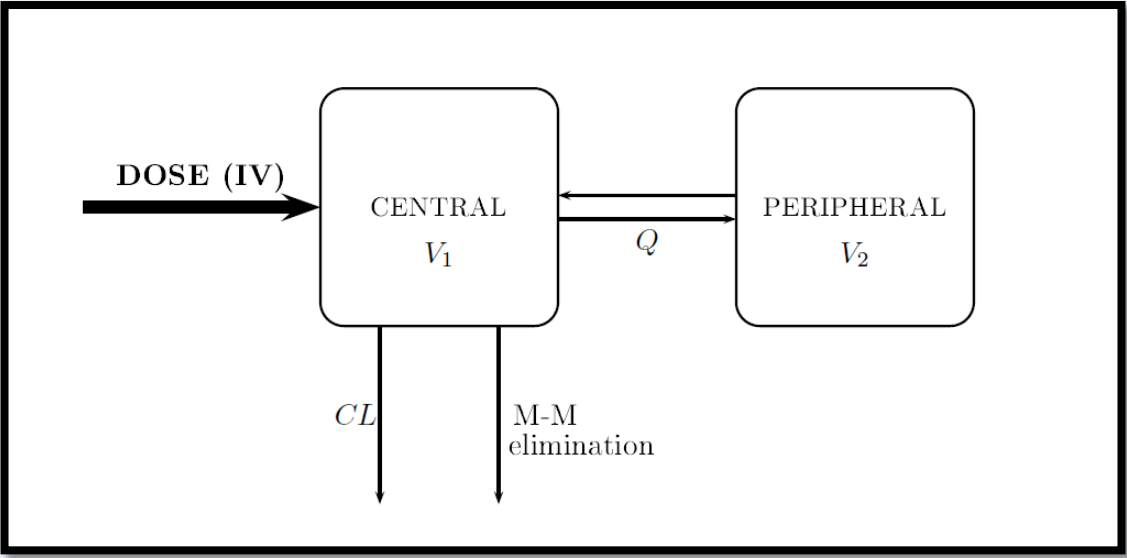


Figure 1. Population PK model

The PK model includes clearance (CL), the volume of distribution of the central compartment (V1) and of the peripheral compartment (V2), the inter-compartmental clearance (Q), the Michaelis-Menten constant (Km) and the maximum elimination rate of the M-M elimination (Vm).

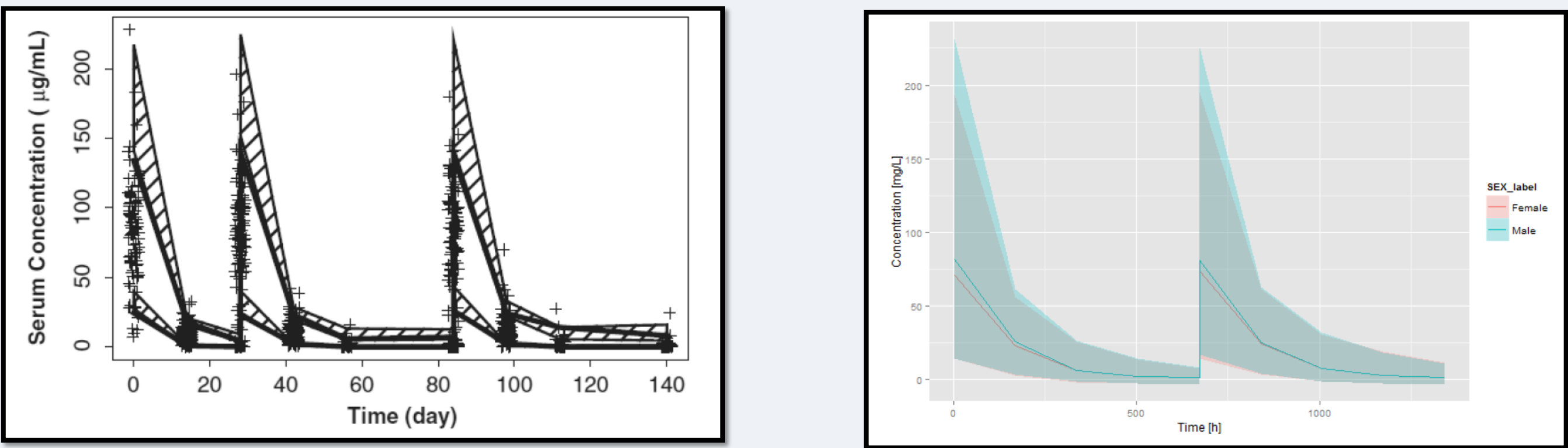


Figure 2. Published (left) and predicted (right) tocilizumab concentration versus time profiles in patients with rheumatoid arthritis and target cohort, respectively.

Agreement between simulated (virtual) cohort and the covariates reported in the publication by Frey et al, 2010.

Covariate	Paper value (median)	Sample population (median)
Albumin (g/L)	38	42
Total Protein (g/L)	74	71
HDL-C (mg/dL)	54	53
BSA (m ²)	1.8	1.8
Creatinine CL (mL/min)	106	108.7

PKPD Model

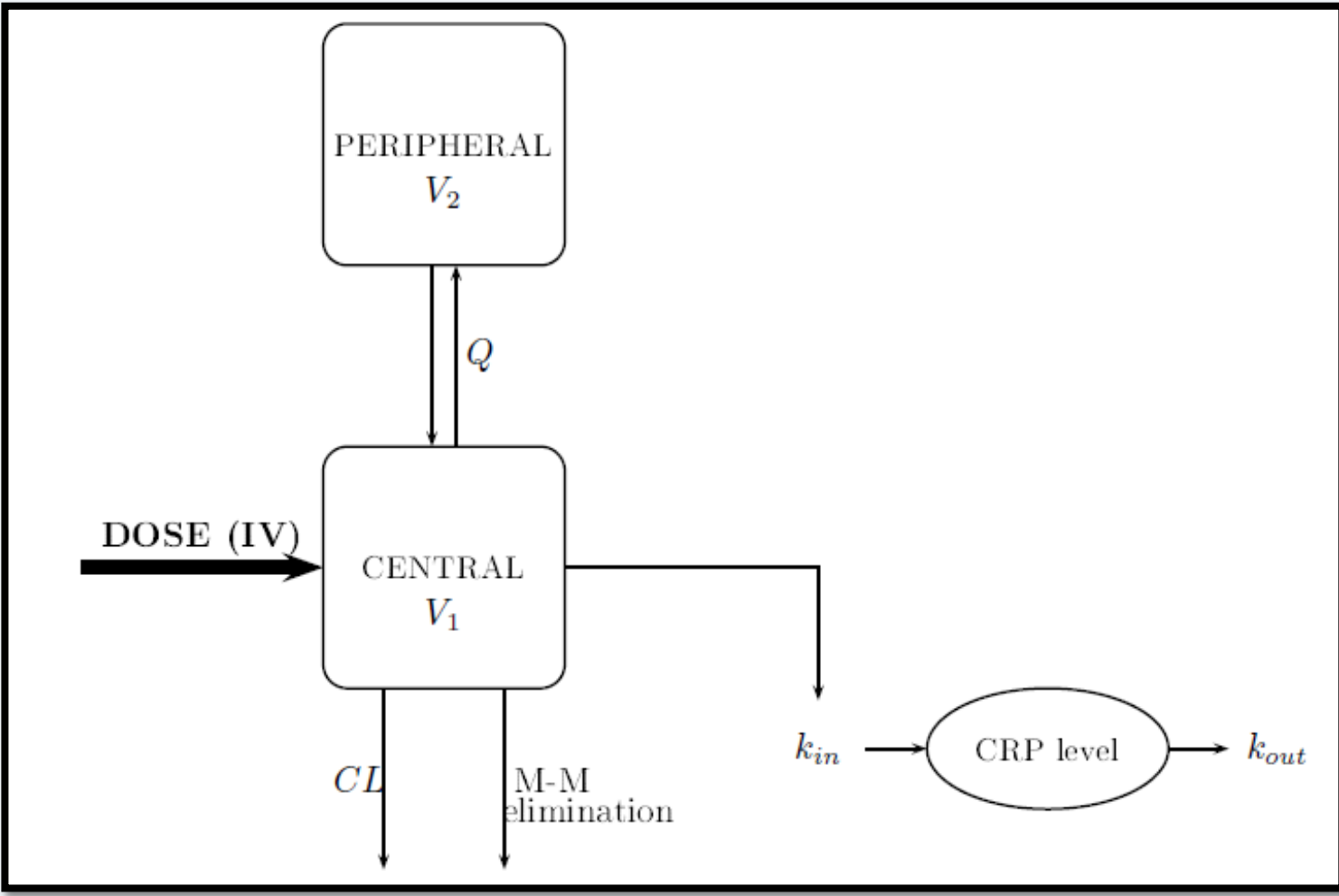


Figure 3. PKPD model describing the inhibitory effects of tocilizumab on circulating CRP levels

Because CRP inhibition is an indirect effect of TCZ, a turnover PD model was used to describe the relationship between TCZ plasma concentration and CRP profiles. A turnover system is defined by two (non-drug-related) parameters, the zero-order rate constant of production k_{in} and the first-order rate constant of degradation k_{out} .

Results

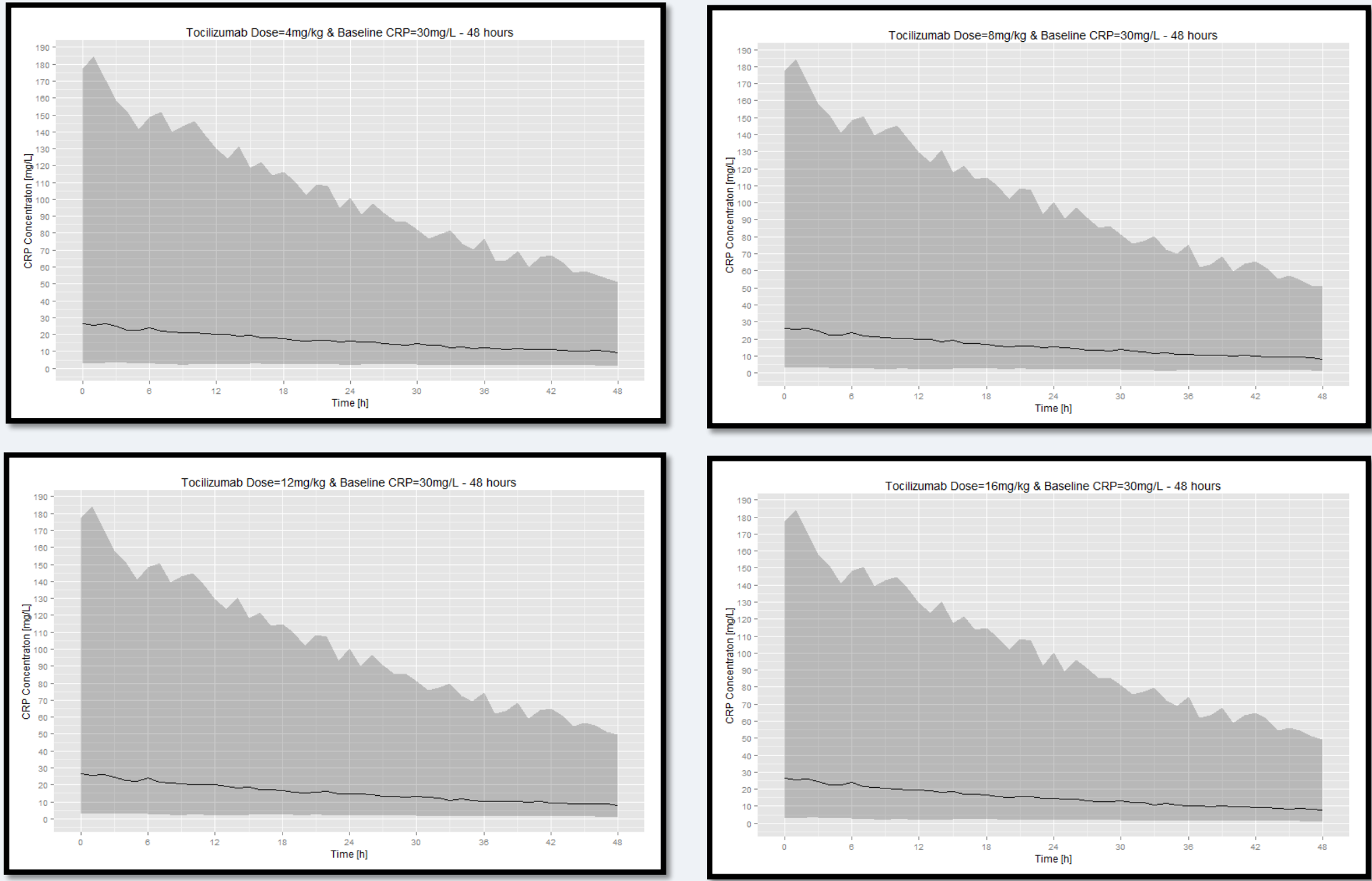


Figure 4. CRP concentration vs. time profiles up to 48 h after administration of single increasing doses of tocilizumab. Lines represent the population median, whereas the shaded area depicts the 90%-confidence intervals.

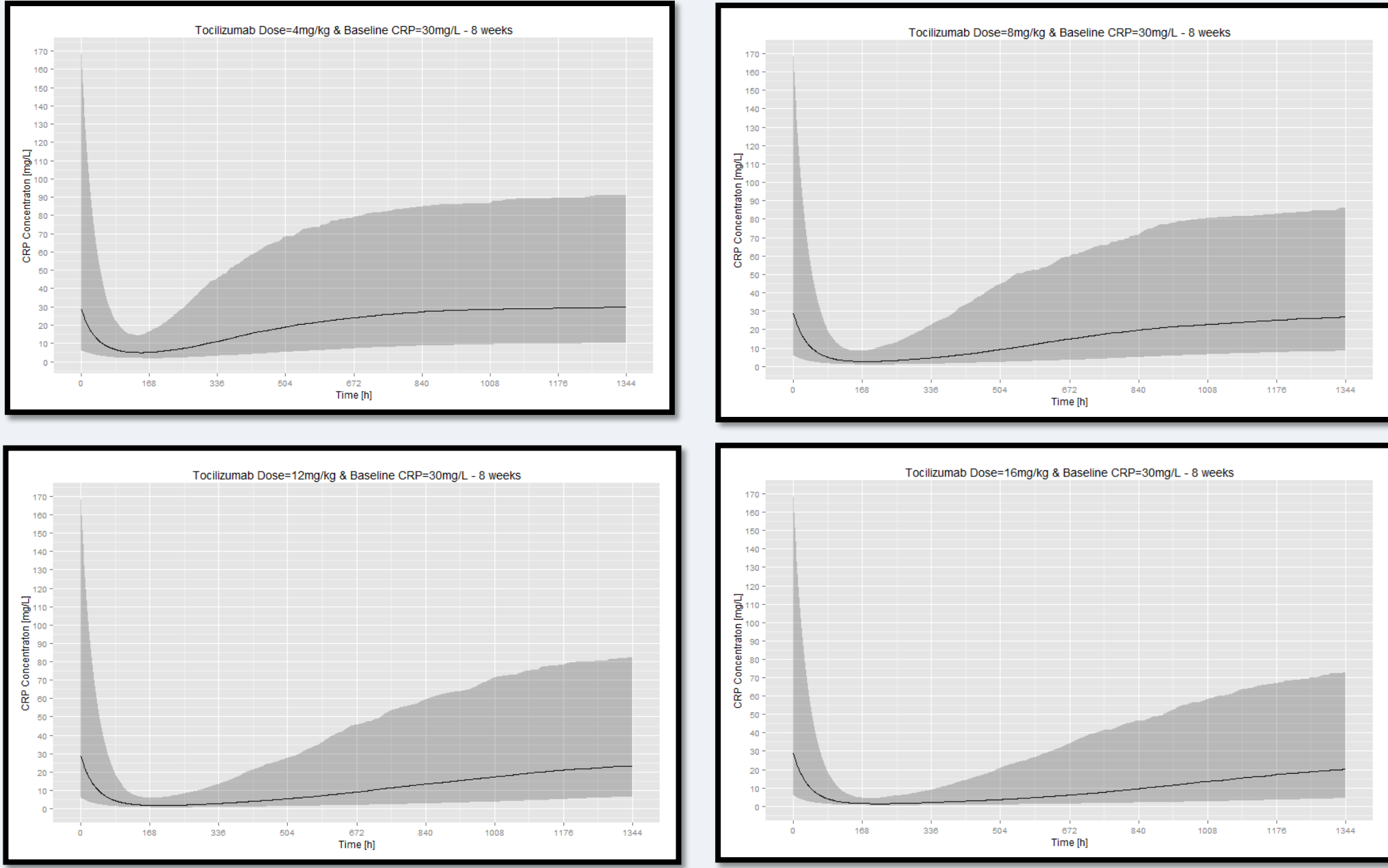


Figure 5. CRP concentration vs. time profiles up to 8 weeks after administration of single increasing doses of tocilizumab. Lines represent the population median, whereas the shaded area depicts the 90%-confidence intervals.

Conclusions

In conclusion, PKPD modelling and simulation has allowed us to inspect the dose rationale for TCZ in a new indication. However, our analysis suggests that CRP inhibition reached within 48h is not maximal. A longer window may be required between dosing and PCA procedures to ensure optimal anti-inflammatory response.

References

- [1] Casas J-P et al. J Intern Med. 2008 Oct;264(4):295-314
- [2] Levi M et al. J Clin Pharmacol. 2013 Feb;53(2):151-9.
- [3] Frey et al. J Clin Pharmacol. 2010 Jul;50(7):754-66.