

Physiologically Based Pharmacokinetic (PBPK) Modeling of Infliximab: Enhancing Treatment Optimization and Clinical Insights in Inflammatory Bowel Disease (IBD)

Z. Petric ¹, P. Paixão ¹, J. Gonçalves ²

¹ Department of Pharmacological Sciences, Research Institute for Medicines, Faculty of Pharmacy, Lisbon, Portugal

² Biopharmaceutical and Molecular Biotechnology Unit, Research Institute for Medicines, Faculty of Pharmacy, Lisbon, Portugal

1. INTRODUCTION

Inflammatory bowel disease (IBD) comprises two distinct yet closely related disorders: Crohn's disease and ulcerative colitis. Infliximab, a monoclonal antibody, is a key treatment for IBD. Its pharmacokinetics and therapeutic effects are influenced by factors such as time-varying inflammatory burden, immunological characteristics, and patient-specific attributes.

Failure to adequately manage an insufficient treatment response can lead to therapeutic failure, primarily due to underexposure [1]. Recently, a subcutaneous formulation of infliximab was introduced to the EU market at a fixed dose of 120 mg, approved exclusively for adult patients [2]. It is intended as a switching option following the intravenous dosing.

2. OBJECTIVE & METHODS

This study assessed whether a fixed subcutaneous infliximab dose (120 mg) is pharmacologically optimal for all adults with IBD, including different body weights (e.g., typical vs. heavy adult), and explored its potential extension to pediatric patients (e.g., older children).

PBPK modeling using PK-Sim® (v11.2) was performed to characterize infliximab pharmacokinetics. The fat compartment was designated as the target organ for subcutaneous administration, with plasma as the target compartment, following a first-order input.

In virtual patients with moderate to severe IBD, an endosomal clearance rate of 1.6 per minute was applied to account for immune and non-immune clearance pathways influencing infliximab disposition and effectiveness.

3. RESULTS

- The baseline PBPK model prediction is shown in Fig. 1
- The PBPK simulation suggests that patients exceeding the typical trial weight (e.g., 120 kg) require higher doses of subcutaneous infliximab (e.g., 240 mg) (Fig. 2).
- While currently approved for adults, older pediatric patients (14 years old, 60 kg) demonstrate similar drug exposure to adults receiving a 120 mg dose (Fig. 3).

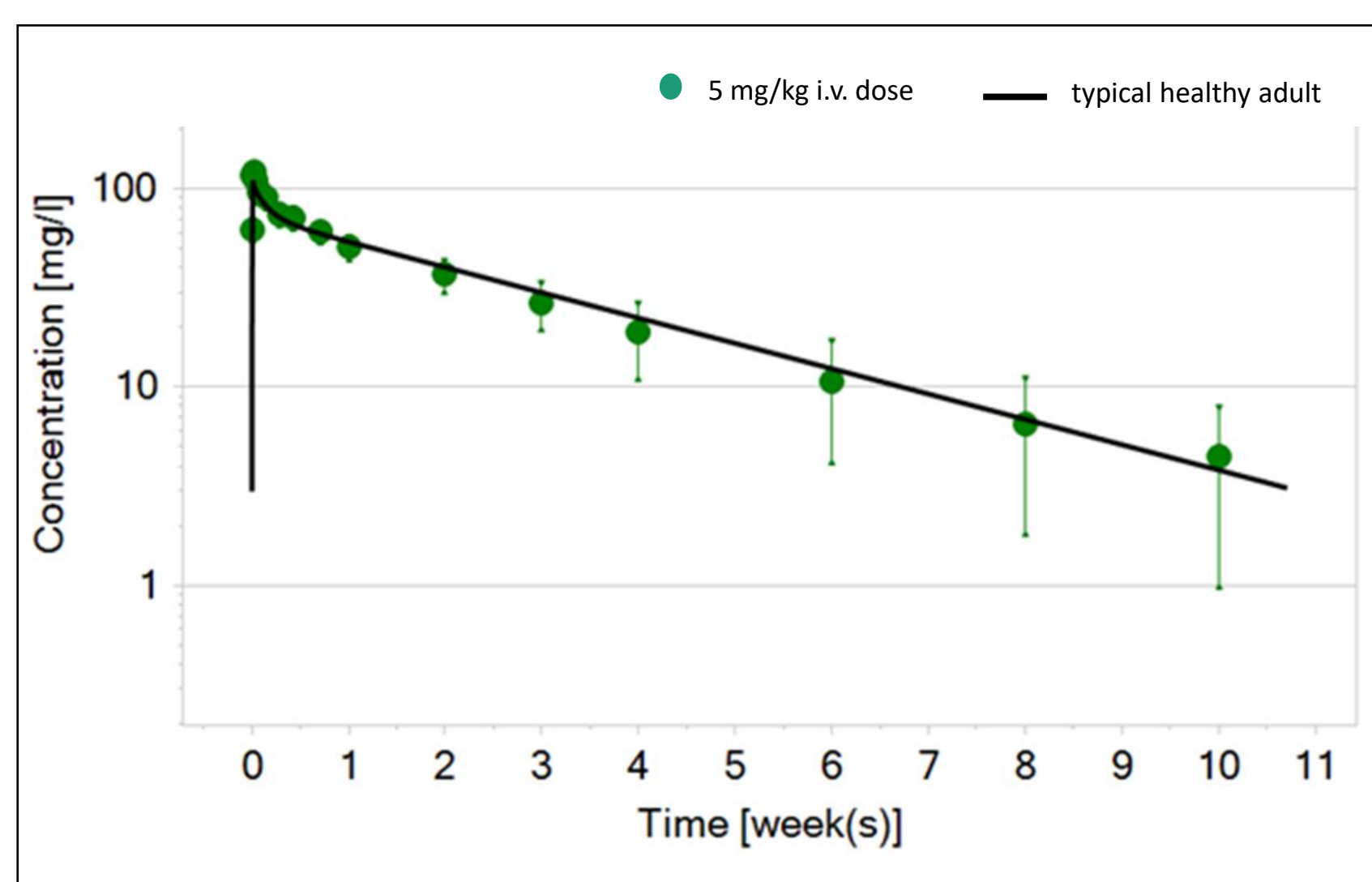


Figure 1. Baseline PBPK model prediction of infliximab on a semi-logarithmic scale for a typical healthy adult (black curve) after a single intravenous treatment (5 mg/kg). The green dots represent the average PK profile digitized from the trial data in healthy adult individuals (see reference [2] for more information).

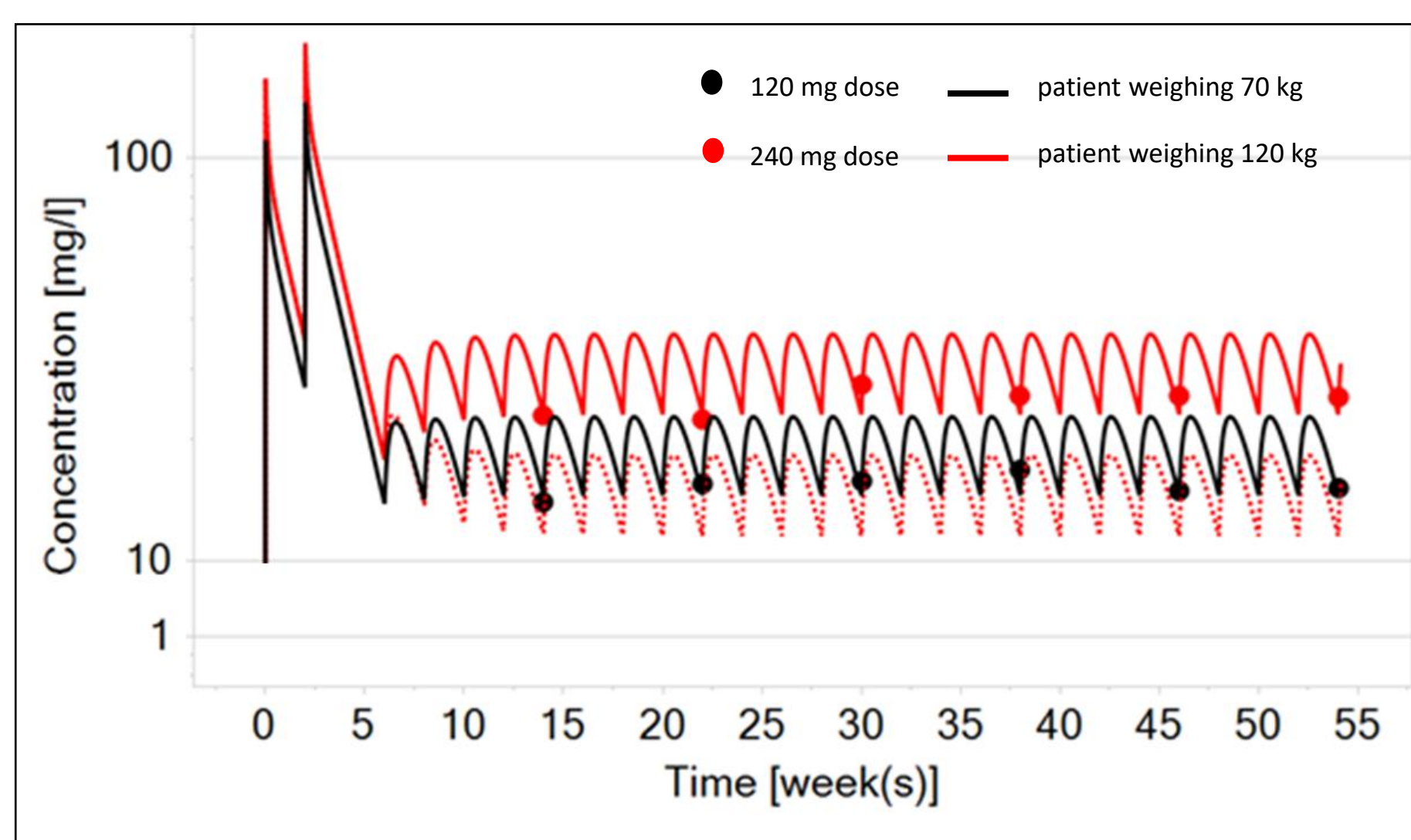


Figure 2. Infliximab PBPK model prediction on a semi-logarithmic scale in adult patients with IBD following a switch to subcutaneous infliximab at week 6. The black curve represents the prediction for a typical (70 kg) individual receiving a 120 mg flat dose of infliximab. The red curve represents the corresponding prediction for a heavier 120 kg individual. Black and red dots indicate the average pharmacokinetic profiles digitized from clinical trial data in IBD patients [2]. The dashed red curve highlights potential underexposure in heavier patients when given a fixed 120 mg dose.

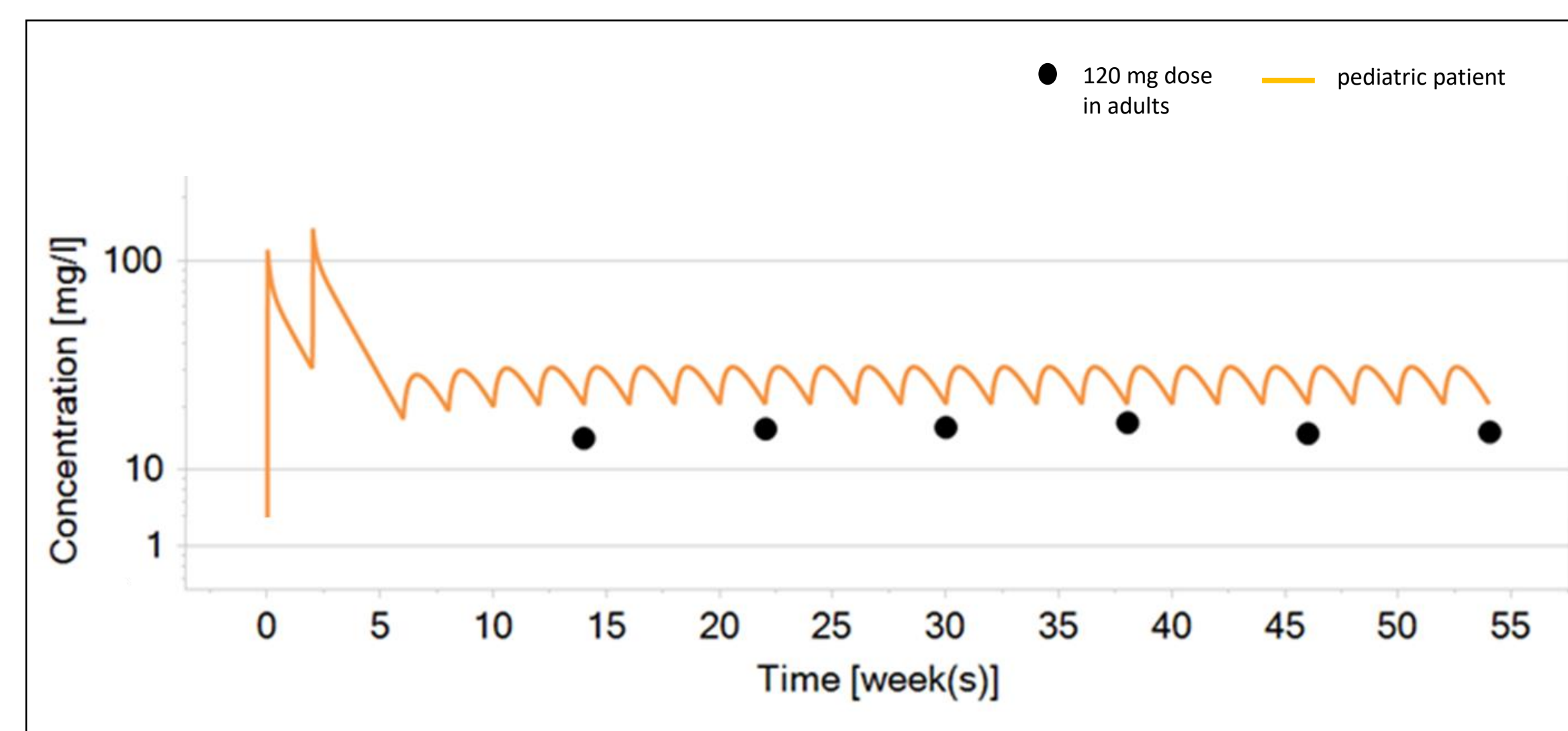


Figure 3. Infliximab PBPK simulation on a semi-logarithmic scale for a typical older child with IBD (14 years old, 60 kg) after switching to a 120 mg subcutaneous dose at week 6 (orange curve). The black dots represent digitized trough concentrations from clinical trial data in adult patients post-switch to 120 mg subcutaneous infliximab. Notice how older children exhibit similar infliximab exposure (in Ctrough) to adults receiving a 120 mg dose.

4. CONCLUSIONS

The approved 120 mg fixed subcutaneous dose of infliximab for adult IBD treatment may be suboptimal for heavier patients, highlighting the limitations of a one-size-fits-all approach to dosing in IBD. However, this dose appears appropriate for older and heavier pediatric patients. These findings support the potential expansion of subcutaneous infliximab approval for pediatric IBD treatment.

The PBPK framework can serve as a valuable tool in clinical pharmacology for advancing insights into IBD treatment optimization.

[1] Petric Z, Gonçalves J, Paixão P. Under the Umbrella of Clinical Pharmacology: Inflammatory Bowel Disease, Infliximab and Adalimumab, and a Bridge to an Era of Biosimilars. *Pharmaceutics*. 2022 Aug 24;14(9):1766. doi: 10.3390/pharmaceutics14091766.

[2] Petric Z, Gonçalves J, Paixão P. Infliximab in Inflammatory Bowel Disease: Leveraging Physiologically Based Pharmacokinetic Modeling in the Clinical Context. *Biomedicines*. 2024 Sep 1;12(9):1974. doi: 10.3390/biomedicines12091974.

[3] Hanzel, J.; Bukkems, L.H.; Gecse, K.B.; D'Haens, G.R.; Mathôt, R.A.A. Population pharmacokinetics of subcutaneous infliximab CT-P13 in Crohn's disease and ulcerative colitis. *Aliment. Pharmacol. Ther.* 2021, 54, 1309–1319.