Close window

PAGE. Abstracts of the Annual Meeting of the Population Approach Group in Europe.
ISSN 1871-6032

Reference:
PAGE 31 (2023) Abstr 10605 [www.page-meeting.org/?abstract=10605]

Population pharmacokinetic model of infliximab in patients with fistulising Crohn's disease

A. Homšek (1), S. Marković (2), D. Kralj (2), O. Odanović (2), P. Svorcan (2), M. Jovanović (1), K. Vučićević (1)

(1) Faculty of Pharmacy – University of Belgrade, Department of Pharmacokinetics and Clinical Pharmacy, Belgrade, Serbia, (2) University Hospital Medical Center "Zvezdara", Gastroenterology and Hepatology Department, Belgrade, Serbia

Ana Homšek

Poster: Drug/Disease Modelling - Other Topics

Introduction: Infliximab (IFX), anti-tumour necrosis factor alpha antibody, is widely used in the treatment of inflammatory bowel diseases. Patients with Crohn's disease may develop a more complicated form which involves fistulae formation, most commonly perianal. IFX has been effective in inducing fistula closure and maintaining disease remission [1]. In order to achieve fistulae healing adequate trough concentrations should be achieved [2].

Objectives:

- Obtaining PK parameters for patients with the fistulising disease form
- Comparing the results to the ones available in the literature for Crohn's disease

Methods: In a retrospective review of medical documentation (from 2013 to present), 42 patients (64% male, 18-65 years old) with fistulising Crohn's disease were selected for analysis. IFX concentrations were measured just before dose administration (trough concentration) or earlier if the patient was experiencing severe disease symptoms. For the majority of patients concentration was measured at week 14, right before the first maintenance dose. Additional concentrations were obtained at scheduled check-ups or after patients experienced signs of relapse. After appropriate premedication, each patient received the calculated fixed dose based on their body weight (dose range was 200-800 mg) via two-hour infusion. The drug was administered according to the standard (week 0, 2 and 6) and accelerated induction (every two weeks) protocols, followed by maintenance therapy (every 4, 6 or 8 weeks). Population modelling approach was applied to characterize pharmacokinetic profile of IFX using NONMEM 7.3 software (ICON Development Solutions Inc., Dublin, Ireland) [3]. The obtained data were processed using Microsoft Excel and R software.

Results: After exclusion of concentrations over the upper limit of quantification (12 μg/mL), a total of 161 concentrations were analysed. IFX concentrations below lower limit of quantification were accounted for using the M5 method [4]. Pharmacokinetics of IFX has, so far, been described by both one- and two-compartment models [5, 6], therefore both were assessed to determine which would best describe the data. Models were evaluated by comparing the objective function values (OFV) as well as goodness-of-fit diagnostic plots and visual predictive checks. A two-compartment model calling ADVAN3 TRANS3 subroutine with first order elimination was selected (OFV 600.03). The estimated values of parameters (with relative standard error) were as follows:

- Clearance = 0.38 L/day (12.4 %)
- Steady-state volume of distribution = 4.26 L (23.2 %)
- Intercompartmental clearance = 0.16 L/day (the value was fixed)
- Central volume of distribution= 1.05 L (the value was fixed)
- Inter-individual variability on clearance = 0.37 (28 %)
- Proportional error = 0.66 (8.6%)
- Additive error = 0.93 (37.8%)

Compared to data available in the literature, the obtained value of IFX CL in our patient population was slightly higher, probably due to disease severity and inflammation status of patients. Therefore, further analysis of covariate effects and exposure-response relationship will be explored in further research.

Conclusion: These preliminary results suggest that patients with fistulising form of Crohn's disease may have higher IFX clearance and since higher trough concentrations are associated with fistulae healing, dose increase and/or dosing interval shortening could be beneficial to achieve disease remission.