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Eugènia Santacana Juncosa, Ariadna Padullés Zamora, Helena Colom Codina, Lorena Rodríguez Alonso, Jordi Guardiola Capo, Jordi Bas Minguet, Núria Padullés Zamora

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Contribution of infliximab population pharmacokinetic model for dose optimization in ulcerative colitis patients

Eugènia Santacana-Juncosa¹, Ariadna Padullés-Zamora¹, Helena Colom-Codina², Lorena Rodriguez-Alonso¹, Jordi Guardiola-Capo¹, Jordi Bas-Minguet¹ and Núria Padullés-Zamora


Correspondence: Eugènia Santacana Juncosa
e-mail: eugenia.santacana@bellvitgehospital.cat;

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Dear Editor,

We read with great interest the paper by Pérez-Pitarch et al. entitled “A pharmacokinetic approach to model-guided design of infliximab schedules in ulcerative colitis patients” (1)¹. They concluded that optimising Infliximab (IFX) doses by Monte Carlo simulation using a previously developed population pharmacokinetic (PPK) model in ulcerative colitis (UC) patient could improve the therapy in these patients. However, we considered appropriate to highlight some aspects of the topic which were not addressed by the authors and according to our experience with therapeutic drug monitoring (TDM) of IFX in patients with inflammatory bowel disease (IBD).

We agree that despite the proven clinical efficacy of anti-tumoral necrosis factor (anti-TNF) agents, treatment failure does occur as primary non-response or secondary loss of response (2)². Although the causes of lack of response to anti-TNF drugs are
multifactorial, the inter- and intra-individual pharmacokinetic (PK) variability plays an essential role. In that sense, two validated PPK models have been published for IFX in IBD patients. These models were developed using data of phase III ACT1 and ACT2 trials for UC (3) and phase III ACCENT I trial for Crohn disease (CD) (4). Briefly, these models consisted on two-compartment models parameterized in terms of central and peripheral distribution volumes (VC and VP, respectively) and distributional and plasma clearances (CLD and CL, respectively). In the CD PPK model, body weight, serum albumin concentration (SAC), presence of antibodies toward IFX (ATI) and concomitant immunosuppressive therapy were identified as the best predictors of interpatient variability. The inclusion of these variables resulted in a greater reduction of unexplained interpatient variability in the final model vs the base model than in the UC population where the statistically and clinically meaningful covariates were SAC, ATI and gender. Both models (3,4) were applied by our group to predict IFX systemic exposure by maximum a posteriori (MAP) Bayesian estimation in IBD patients of our hospital. The non-linear mixed-effects modelling (NONMEM) program v7.2 (Icon Development, Ellicott City, USA) was used for that purpose. Bias and imprecision were calculated to assess the predictive performance of both PPK models in each patient population. Prediction of IFX individual concentrations (Cipred) in both populations (UC and CD) by using the CD PPK model led to a non-significant overall mean relative bias of -3.99% (IC95%: from -6.9 to 14.9%) and an acceptable imprecision of 18.96% (IC95%: 8.5-29.39). Moreover a good correlation was found (R-sq = 0.9209, p < 0.0001) between the observed (Cobs) and Cipred (Fig. 1). On the contrary, a bad prediction was found when the UC PPK model was applied in UC patients for the same purpose (R-sq = 0.6851). Therefore, the CD PPK model is, until now, the best tool to support dose tailoring during the TDM of IFX in patients of both populations. Hence, further studies will be needed to improve the actual UC PPK model to be used for Bayesian prediction in IBD patients and dose optimization.

References
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Fig. 1. Correlation between observed and individual predicted concentrations in CD and UC patients using the CD PPK developed model. Circles are IFX concentrations, red line is the identity line and the black one is the line describing the general trend of the data.