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Validation of a population pharmacokinetic model of adalimumab in a cohort of patients with inflammatory bowel disease

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ABSTRACT

Background: therapeutic monitoring of anti-TNF drugs and anti-drug antibody levels are useful for clinical decision-making, via the rationalization and optimization of the use of anti-TNF treatments. The objective of the present study was to validate the model of Ternant et al., in a cohort of patients with inflammatory bowel diseases (IBD). This model was originally established for patients with rheumatoid arthritis and was used in this study to optimize the adalimumab (ADA) dose and predict ADA trough levels (ATL).

Methods: this study used concentration data points from 30 IBD patients who received ADA treatment between 2014 and 2015. A goodness-of-fit of the model was determined by evaluating the relationship between the observed ATL values and population model-predicted values (PRED) or individual model-predicted values

(IPRED).

Results: a total of 51 ADA concentration points were analyzed. The bias of the model was 2.39 (95% CI, 1.63-3.15) for PRED and 0.63 (95% CI, 0.23-1.03) for IPRED. The precision was 3.57 (95% CI, 2.90-4.13) and 1.53 (95% CI, 1.22-1.80), respectively.

Conclusions: therapeutic drug monitoring involving ATL may allow the optimization of the treatment of IBD patients. The validation results of the pharmacokinetic (PK) model for ADA in IBD patients are inadequate. However, additional studies will strengthen the bias and precision of the model.

Key words: Pharmacokinetic model. Adalimumab. Inflammatory bowel diseases. Trough levels.

INTRODUCTION

The development of agents that target the tumor necrosis factor α (anti-TNF) has greatly changed the paradigm of the treatment of inflammatory bowel diseases (IBD) (1). Adalimumab (ADA) and infliximab (IFX) have been demonstrated to be effective agents in the induction and maintenance of clinical remission in IBD patients (2-4). However, approximately 10 to 30% of patients do not achieve an effective response with the initial treatment of anti-TNFs, i.e., a primary non-response (5-7). The secondary non-response (loss of response over the time) is around 13% and 20% of patients per year of treatment with IFX or ADA, respectively (5,8-10). Factors implicated in the response to anti-TNFs include patient (smoking habits, weight) (11,12), disease (phenotype, duration) (5,13), drug (pharmacokinetic, pharmacodynamic) (10) and treatment (dosing, combination therapy) (5,14) related variables. Immunogenicity is also a mechanism involved in the primary and secondary non-response to anti-TNFs (7). The formation of antibodies against ADA or IFX has been shown to compromise their biological activity by blocking the binding to their targets and accelerating their clearance (10,15,16). The functional concentration of anti-TNFs is therefore diminished and their half-life is shortened (17,18). Moreover, the risk of hypersensitivity reactions increases with the formation of the immune complexes (19). The incidence of immunogenicity reaches values of up to 9% and 18%

for ADA and IFX, respectively (20-22). Therapeutic monitoring of anti-TNF drugs and anti-drug antibody levels has been demonstrated to be useful in clinical decision-making. They allow the rationalization and optimization of the use of anti-TNF treatments such as dose intensification, addition/switching of immunomodulators, switching of anti-TNF agent and swapping to an agent with a different mechanism of action (23,24). An adequate population pharmacokinetic (PK) model is necessary in order to describe the kinetic behavior of a drug in a large cohort of patients due to the inter-individual variability observed with anti-TNFs (25). The PK model of Fasanmade et al. (26) was established for IFX in children and adult patients with Crohn's disease, and is probably the most appropriate model for monitoring biological drugs in IBD patients. Ternant et al. (27) developed a PK model for ADA in a cohort of patients with rheumatoid arthritis (RA). Ternant et al. (28) also published a brief study of a post-hoc analysis of 65 patients with Crohn's disease receiving ADA. However, the number of descriptive variables in the PK model was relatively low and the publication was a short communication (included as a letter to the editor). For this reason, this study focused on the model for RA (27). The objective of the present study was to validate the model of Ternant et al., (27) in a cohort of IBD patients. This model was originally designed for RA patients and was used here to optimize the ADA dose predict ADA trough levels (ATL).

MATERIAL AND METHODS

This validation study used concentration data points from 30 IBD patients who received ADA treatment between 2014 and 2015 and attended the IBD Unit at the Hospital de Manises (Valencia, Spain). Demographic, clinical and pharmacokinetics data of patients were collected from medical records. The ADA dose scheme was an initial dose of 160 mg that switched to 80 mg two weeks later and maintained at 40 mg every two weeks thereafter. Both ADA and albumin concentrations were determined by collecting blood samples from patients during the maintenance phase, with a steady-state adalimumab status. Each sample was collected before the corresponding administration of ADA. Samples were analyzed using a validated sandwich enzyme-linked immunosorbent assay (Promonitor®-ADA, Grifols). The ADA monoclonal

antibody was detected by a specific antibody conjugated to horseradish peroxidase (27). Briefly, a plate was coated with recombinant human TNF- α and detection was performed using a biotin-labeled monoclonal antibody. The concentration of ADA was measured by a colorimetric reaction (450 nm). Lower and upper limits of ADA quantification were 0.25 and 12.0 $\mu\text{g/ml}$, respectively. All patients were in clinical remission when ADA levels were determined. None of the patients received a dose intensification or spacing of the doses.

Validation of the pharmacokinetic model

The population model of Ternant et al. (27) for RA consisted of a one-compartment model with first-order absorption and elimination rates. One- and two-compartment models with first-order absorption, distribution and elimination rates were also tested during the model development. The apparent volume of distribution and clearance were the estimated PK parameters; they are apparent values due to the fact that the administration of ADA was subcutaneous. Structural models were compared using the Akaike information criteria (AIC). The AIC was defined as $-2LL + 2p$, where $-2LL$ is the minus 2 log likelihood and p is the number of estimated parameters from the model (29). The selected model had the lowest AIC (the best-fitting model). No parameters were identified for the peripheral compartment. The proportional residual error model was selected. Weight and sex had a significant impact on clearance according to the univariate analysis, i.e., it was greater with a higher weight and male sex. The predictive ability of the model by Ternant et al. (27) for RA was validated in terms of bias and precision. Bias, referred to as the constant bias of the prediction model, was measured as the mean of the absolute errors (mean prediction error, MPE) with the 95% confidence interval (95% CI), according to Berends et al. equations (30):

$\text{MPRE} = \frac{1}{n} \sum_{i=1}^n |C_{\text{obs}} - C_{\text{pred}}|$; C_{obs} and C_{pred} indicating the observed and predicted concentration value ($\mu\text{g/ml}$), respectively.

Precision, referred to as the dispersion of predictions with respect to observed values, was measured as the root mean squared prediction error (RMSPE) and the 95% CI, according to Berends et al. equations (30):

RMSPE =

Values of precision may be interpreted as an estimation of the typical deviations of the distribution of errors in the prediction. Both parameters were determined for the observed concentrations compared with both population model-predicted (PRED) and individual model-predicted (IPRED) values. The PRED values were obtained by applying the PK model, with influencing co-variables such as sex and weight. By contrast, IPRED values were calculated using a post-hoc Bayesian estimation, taking into account observed plasmatic concentrations. Relative errors of PRED and IPRED were expressed as parts per unit. The goodness-of-fit of the model was determined by evaluating the relationship between the observed ATL values and PRED or IPRED. Bias and precision were estimated for PRED and IPRED values to demonstrate the improvement in the adjustment of the model when including the observed plasmatic concentration data. The Bayesian methodology was also used.

Statistical analysis

Quantitative variables were expressed as absolute and relative (%) frequencies and qualitative variables were expressed as the median with the interquartile range (IQR) and 95% confidence interval (95% CI). If zero was included in the 95% CI of MPE or RMSPE, no significant bias was present. The correlation between observed and predicted values was measured using a Pearson's correlation analysis. Simulation and estimation of the population and individual pharmacokinetic parameters and the plasmatic concentrations estimated *a priori* with the population model and *a posteriori* with Bayesian estimation were performed using the NONMEM 6.0 software (ICON plc®). All statistical analyses were performed using the SPSS 19.0 software.

Ethical considerations

All procedures were approved by the Research Committee of the Hospital de Manises.

RESULTS

Patients

Data from 30 patients were included in the study. Patients were predominantly female (53.3%) with a median age of 42 years (IQR, 30-59 years), an average weight of 58.5 kg (IQR, 45.0-75.0 kg) and non-smokers (76.7%) with Crohn's disease (83.3%). Demographic and clinic characteristics of patients are shown in table 1. A total of 53.3% of patients received azathioprine as concomitant immunomodulator treatment. Half of patients were naïve to biological treatment. In contrast, 33.3% and 16.7% had previously switched from IFX therapy due to a non-response or immunogenicity, respectively. The median plasma albumin level was 4.3 g/dl (IQR, 4.0-4.6 g/dl).

Validation of the model

A total of 51 ADA concentration points were obtained from patients, i.e., two determinations from almost all patients at weeks 8th and 14th. One data point with a value higher than 12.0 µg/ml was considered as an outlier and was excluded from the analysis. Goodness-of-fit plots showed the relation between the observed ATL values and PRED or IPRED indicated that the model adequately described the data (Fig. 1). Estimated pharmacokinetics parameters of ADA are shown in table 2 and the plasma clearance of ADA was 0.22 l/day (IQR, 0.19-0.29 l/day). The volume of distribution was 7.8 l (IQR, 6.0-11.5 l). The distribution (Fig. 2A) and frequency (Fig. 2B) of observed adalimumab concentration values indicated that absolute errors for PRED and IPRED increased with the observed ATL values ($r = 0.78$ and $r = 0.68$, respectively). This relationship was heteroscedastic, meaning that imprecision increased with higher values of the parameter. Thus, relative errors were also analyzed. Relative errors remained stable for PRED and partially stable for IPRED *versus* observed values. Therefore, the analysis was also performed with relative errors for PRED and IPRED. The average absolute error for PRED and IPRED was 2.39 (95% CI, -2.8-7.0) and 0.629 (95% CI, -2.2-3.0), respectively. The MPE for the absolute error in PRED and IPRED was 2.39 (95% CI, 1.63-3.15) and 0.63 (95% CI, 0.23-1.03), respectively. The MPE for the relative error was 26.41% (95% CI, 14.66-38.16) and 3.60% (95% CI, -3.96-11.17%). The RMSPE for the absolute error in PRED and IPRED was 3.57 (95% CI, 2.90-4.13%) and 1.53 (95% CI, 1.22-1.80), respectively. Finally, RMSPE for the relative error was 49.71% (95% CI, 40.00-56.09%) and 26.62% (95% CI, 15.26-34.41%).

DISCUSSION

Strategies aimed to prevent non-response to anti-TNFs are necessary due to the incidence of primary and secondary non-responses. Prevention in clinical practice is achieved using concomitant immunomodulator therapies, pre-treatment with corticoids, optimization of drug dose or drug use in a regular and maintained manner (31). Therapeutic monitoring of anti-TNF drug and anti-drug antibody levels are also a promising useful tool for clinical decision-making. Elevated anti-TNF levels correlate with remission and clinical response (32,33). Increased anti-drug antibody levels have been associated with lower anti-TNF levels, loss of response and hypersensitivity reactions (15,18,19). The algorithms available in the literature are based on anti-TNF drug levels (34-36). Nevertheless, they have not been designed to individualize the dose treatment in patients with sub- or supra-therapeutic trough levels. For this reason, further monitoring of anti-drug antibody levels and the definition of an optimal trough level are necessary to achieve clinical remission and mucosal healing. Sharma et al. (37) developed a population PK model based on 189 pediatric patients with moderate-to-severe CD who received ADA for induction and maintenance. This study showed a relationship between a higher body weight and the presence of antibodies against ADA with a greater ADA clearance. Berends et al. (30) evaluated 96 patients with CD who received ADA for induction and maintenance using some models previously described in the literature. This study showed that none of them fitted with ADA PK in their patient series.

Our study aimed to develop a PK model for anti-TNF in patients with IBD that allowed an optimization of the drug dose and the prediction of trough levels. We proposed a model for IFX based on these assumptions that was adapted from Fasanmade et al., (26) and for ADA that was adapted from Ternant et al. (27). We believe that it is important to validate the PK model in different populations in order to confirm the reproducibility. In fact, we had previously validated the model of Fasanmade et al. for patients with IFX (Juan G, Alvariño A, Oltra L, et al. *Utility of "trough levels" determination and anti-infliximab antibodies in patients with inflammatory bowel disease*; European Crohn's and Colitis Organization, 2014. Poster 302). In the present

study, we present a validation of the PK model of Ternant et al. (27) that was adapted to our cohort of IBD patients. With regard to the goodness-of-fit of the model, the concordance of observed and predicted ATL levels was worse than that reported in patients with RA, especially in PRED (26,27). The biases of the model were 2.39 for PRED and 0.63 for IPRED, whereas the precision was 3.57 and 1.53, respectively. The bias and precision were also worse than those observed in RA patients. In fact, the confidence intervals of relative errors in IPRED reached up to 34%, indicating an unacceptable precision (38). Several causes may explain the limited results obtained. First, the original model of Ternant et al. (27) was developed for patients with RA. Even though they are immune-mediated diseases, the model is probably disease- and patient-specific. Potential differences may exist in drug disposition for effectiveness requirements, as already suggested by Fasanmade et al. (26). In fact, both RA and IBD significantly differ in the effect of concurrent immunomodulator treatment and immunogenicity (39,40). Second, the number of covariates may be insufficient to explain the inter-individual variability or, in line with the first point, covariates for RA may not be useful for IBD. Covariates included in the original model of Ternant et al. (27) were sex and body weight. However, the final population model of Fasanmade et al. (26) of IFX in Crohn's disease patients included body weight, baseline serum albumin concentration, immune response status and concurrent immunomodulator treatment. The addition of albumin concentration to the model of ADA in patients with IBD would probably improve the results obtained herein due to its important role in the clearance process of anti-TNFs drugs. Third, the number of patients included in our study was low; 30 patients and 50 effective concentration points. The model of Ternant et al. included 30 patients with 129 available concentration points (27) and the model of Fasanmade et al. included 692 patients and 5,757 concentration data points (26). Moreover, it is also important to consider that half of our patients were naïve to anti-TNF treatments, 33% were non-responders to previous anti-TNF treatments and 16.7% failed IFX by immunogenicity. A total of 53.3% also received a concomitant immunomodulator treatment. All of these patient characteristics could have impacted on the model, for example in the clearance, increasing the inter-individual variability and thus weakening the precision. In fact, all patients were naïve to anti-TNF

treatments and were receiving concurrent treatment with methotrexate the model of Ternant et al. (27). This may have impacted on the kinetic behavior of ADA. Therefore, the main limitation of the study was related to the influence of the immune-mediated pathology on the kinetics of the biological drug, as demonstrated by Passot et al. (41). Since all our patients were in clinical remission, the validation of the model was performed independently from the severity and activity of the disease. Despite the limitation of our results, the goal of our study was to validate the process of the adapted model of Ternant et al. (27) in a cohort of IBD patients. In our opinion, the method of external validation used in this study is adequate as a preliminary step to establish a therapeutic monitoring program using Bayesian methodology with population PK models for the individualized adjustment of the ADA dose. An internal validation of population models and the definition of bias and precision before evaluating their clinical use are important due to the methodological limitations of the present study and the difficulty to extrapolate results from other diseases. We would also like to highlight the added value of including population PK models with Bayesian estimations in the decision-making that aimed to individualize dose regimens, either in intensification and de-intensification strategies. Mould et al. (42) recently indicated the possibility to reduce the variability of the exposure to the biological drug by maintaining patients within a target therapeutic range over a longer period than conventional dosage strategies. Further studies with more specific covariates, a larger patient cohort and more ATL data are required to explain the inter-individual variability of ADA for dose individualization.

In conclusion, therapeutic drug monitoring with ATL may allow the optimization of treatment in IBD patients. The validation results of our PK model for ADA in IBD patients are inadequate. However, additional studies will strengthen the bias and precision of the model.

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Table 1. Demographic and clinic characteristics of patients

	<i>Total patients (n = 30)</i>
Sex male, n (%)	14 (46.7)
Age, mean years (IQR)	42 (50-29)
Weight, median kg (IQR)	58.5 (75.0-55.0)
Smoking habits, n (%)	
Smoker	4 (13.3)
Ex-smoker	3 (10.0)
Non-smoker	23 (76.7)
Diagnosis, n (%)	
Crohn's disease	25 (83.3)
Ulcerative colitis	5 (16.7)
Concomitant immunomodulator treatment, n (%)	
Azathioprine	16 (53.3)
Methotrexate	1 (3.3)
6-mercaptopurine	1 (3.3)
None	12 (40.0)
Previous biological treatments, n (%)	
None	15 (50.0)
IFX (non-responder)	10 (33.3)
IFX (failure by immunogenicity)	5 (16.7)
Plasma albumin levels, median g/dl	4.3 (4.0-4.6)

IQR: interquartile range.

Table 2. Estimated pharmacokinetics parameters of ADA

<i>Median (IQR)</i>	<i>Total patients (n = 30)</i>
Plasma clearance (l/day)	0.22 (0.19-0.29)
Half-life (days)	26.6 (14.8-34.9)
Area under the curve (mg*d/l)	118.7 (92.2-136.5)
Steady-state volume of distribution (l)	7.8 (6.0-11.5)
Mean trough levels (µg/ml, 95% CI)	6.64 (5.78-7.50)

IQR: interquartile range; 95% CI: confidence interval 95%.

Goodness-of-fit plots between observed ATL values and PRED or IPRED

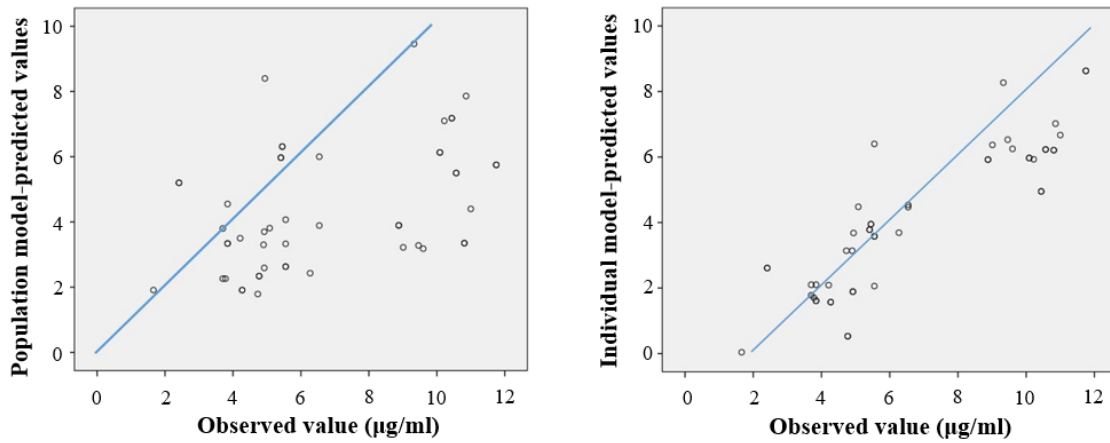


Fig. 1. Goodness-of-fit plots of the model showing the relationship between the observed values of adalimumab concentrations and population and individual model-predicted values. ATL: Adalimumab trough levels; PRED: population model-predicted; IPRED: individual model-predicted.

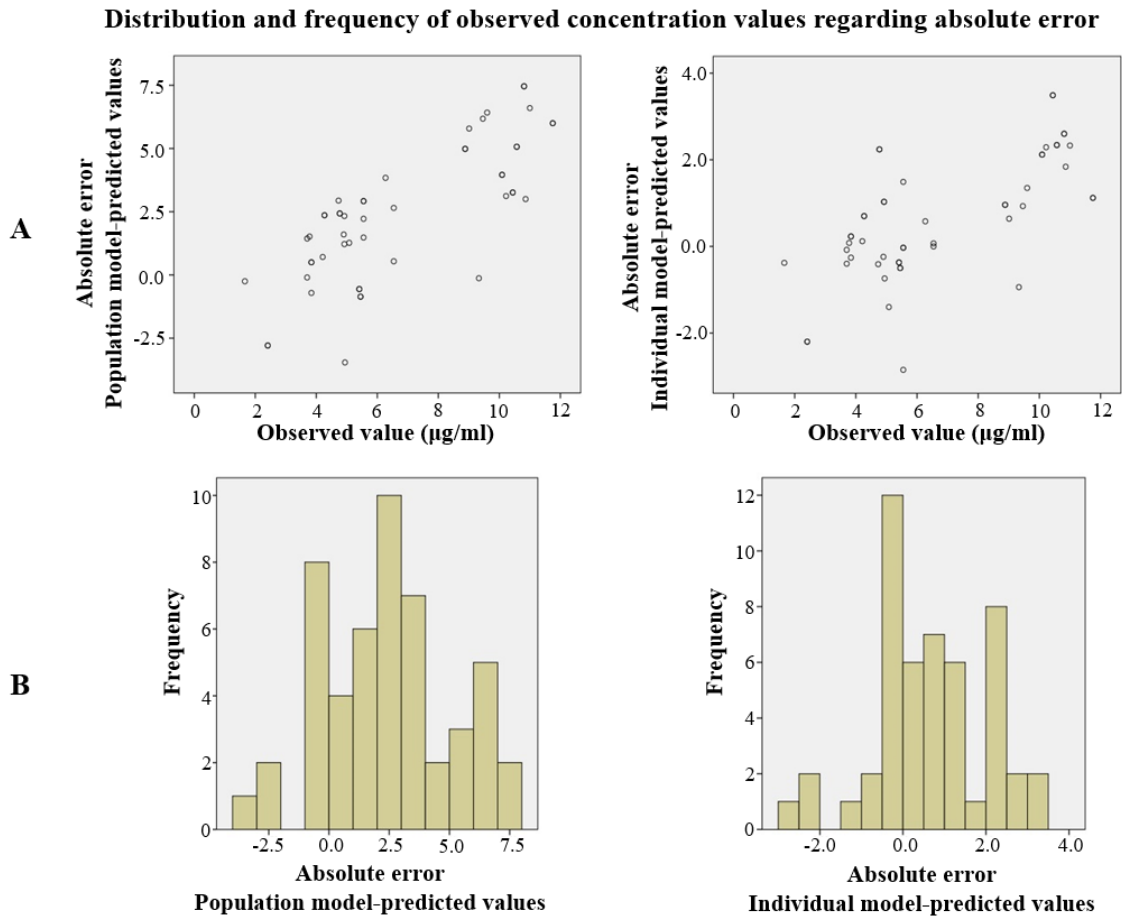


Fig. 2. Distribution (A) and frequency (B) of the observed values of adalimumab concentrations with regard to the absolute error for population and individual model-predicted values.