Usefulness of therapeutic drug monitoring of infliximab during the induction period in patients with inflammatory bowel disease

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ABSTRACT

Introduction: previous studies have shown that higher infliximab trough levels are associated with favorable short-term and long-term therapeutic outcomes in inflammatory bowel disease. There is a need to determine which patients could benefit from proactive therapeutic drug monitoring in the induction phase. The aim of this study was to evaluate the pharmacokinetic variability of infliximab, determine the factors associated with achieving target infliximab trough levels in the induction phase and analyze the clinical and biochemical response at week 26 of treatment.

Patients and methods: a retrospective observational study was performed of patients with inflammatory bowel disease and data available on serum levels of infliximab during the induction period. The percentage of patients that achieved target infliximab trough levels at week 6 was determined. Clinical remission and response and biochemical remission were evaluated at week 26.

Results: thirty patients were included and only 13 (43.3 %) had infliximab trough levels > 15 µg/mL at week 6. A clinical response was observed during the maintenance period in 71.4 % of patients, their infliximab levels were significantly higher than in non-responders (6.3 µg/mL [IQR: 6.7] *vs* 1.0 µg/mL [IQR: 5.0], respectively; p = 0.016). Likewise, 53.6 % of patients achieved biochemical remission (responders 6.2 µg/mL [IQR: 5.2] *vs* non-responders 3.2 µg/mL [IQR: 5.0]; p = 0.031).

Conclusion: less than half of patients had target infliximab levels during the induction period. Therapeutic drug monitoring during this period is related to the achievement of therapeutic levels of infliximab and may lead to a better clinical response in these patients.

Keywords: Infliximab. Inflammatory bowel disease. Therapeutic drug monitoring. Induction.

INTRODUCTION

The effectiveness of infliximab, the first anti-TNF-α (tumour necrosis factor alpha) drug approved for the treatment of Crohn's disease (CD) and ulcerative colitis (UC), has been demonstrated by numerous studies (1-3). However, it has been noted that around 30 % of patients with inflammatory bowel disease (IBD) show a primary non-response to biological therapies (4-6). Over time, around 50 % of patients discontinue the treatment due to the loss of secondary response or even the appearance of adverse effects (4,7). A loss of response has been associated with pharmacokinetic processes (i.e. the presence of antibodies or low or undetectable levels of the drug, perhaps due to drug clearance) or pharmacodynamics (probably related to a non-TNF-mediated inflammatory disease phenotype) (8,9). The difficulty to achieve high infliximab trough levels (ITLs) is due to factors present in individual patients that affect the pharmacokinetics of infliximab (interindividual variability), which is a key factor in both primary and secondary failures (10,11).

Therapeutic drug monitoring (TDM) has become increasingly important in the management of IBD due to its ability to detect early non-responders and can allow for the individualized optimization of therapy (12,13). Certain studies

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have shown a positive correlation between infliximab levels at induction and favorable therapeutic outcomes during the maintenance period (14-17). Furthermore, studies such as Papamichael et al. (18) suggest that proactive TDM after induction and during maintenance therapy can improve the efficacy of anti-TNF treatment. Moreover, the implementation of population pharmacokinetic models with Bayesian estimates in decision-making has added value to individualize dose regimens. The pharmacokinetic model of Fasanmade et al. (11) was established for infliximab in children and adult patients with CD, and is probably the most appropriate model for monitoring biological drugs in IBD patients (19,20).

Hypothetically, maintaining high drug trough levels in the induction period can prevent primary non-response to biologic agents (21). Thus, we believe it is important to know the prevalence of low infliximab levels in the induction phase and identify which patients could be candidates for TDM. Therefore, the primary outcome of the study was to evaluate the pharmacokinetic variability of infliximab and to determine the factors associated with achieving the target ITL in the induction phase. The secondary outcome was to analyze the relationship between ITL and the clinical and biochemical response at week 26 of treatment.

PATIENTS AND METHODS

Study design and patients

This retrospective observational study was performed from January 2017 to December 2018 in a hospital in Murcia (SE Spain), which provides medical care to 200,892 patients. The inclusion criteria were outpatients with IBD, age > 16 years, who had received an induction dose of 5 mg/kg at 0, 2 and 6 weeks. Patients without ITL during the induction period (week 6) or those without information relating to their clinical responses or laboratory parameters were excluded. The study was approved by the local Ethical Research Committee.

The following demographic and clinical data were recorded: sex, age, body weight, diagnosis, disease behavior and location according to the Montreal Classification at diagnosis (22), perianal disease, previous biological and steroidal therapy, the use of concomitant immunosuppressive therapy, biosimilar infliximab treatment, biochemical parameters including albumin, C-reactive protein (CRP) and faecal calprotectin (FCP), modified Harvey-Bradshaw index (mHBI) and the basal partial Mayo Score.

Serum infliximab trough levels

ITLs were determined from serum samples collected prior to infusion at week 6 (induction period) and week 26 (maintenance period). The serum samples were separated into two aliquots and frozen within 2 h of collection. Serum ITLs and antibodies to infliximab (ATI) were determined using a commercially available validated enzyme-linked immunosorbent assay (ELISA) kit (Promonitor; Grifols, Spain), following the manufacturer's instructions. The lower limit of quantification for the presence of infliximab was 0.035 mg/L. This method did not allow for thr detection of ATI in the presence of infliximab. The lower limit of quantification of ATI was 5 AU/mL.

Pharmacokinetic variability and dose adjustment at week 6

The percentage of patients with target ITL in the induction phase was determined. Trough levels > 15 µg/mL at week 6 were considered optimal (17).

A Bayesian prediction with NONMEM software (version 7.3.0; Icon Development Solutions Ellicott City, MD, USA) based on the population pharmacokinetic model developed by Fasanmade et al was used to determine the individual pharmacokinetic parameters of each patient (11). These parameter estimates were used to predict steady state ITL, which could be reached by not intensifying the dose regimen after induction. Subsequently, the cut-off point of the elimination half-life was estimated to predict ITL > 3 µg/mL in the steady state (maintenance phase).

In order to guarantee levels in the therapeutic range in the maintenance phase, post-induction dose adjustment was performed according to a Bayesian pharmacokinetic model and clinical criteria by a multidisciplinary team (formed by two gastroenterologists specializing in IBD and a hospital pharmacist specializing in clinical pharmacokinetics). The dose intensification performed consisted of interval reduction, a dose increase or both.

Pharmacokinetics and clinical outcomes at week 26

Pharmacokinetic outcomes were determined by calculating the percentage of patients that achieved ITL in the target therapeutic range (3-10 µg/mL) (23) at week 26. We evaluated the clinical response at week 26 (6 months) using the HBI or partial Mayo Score. Clinical remission was defined as HBI < 5 for patients with CD or a Mayo Score < 2 for patients with UC. Clinical response was defined as a decrease in mHBI by > 3 points or a decrease in partial Mayo Score by > 2 points (24). Biochemical remission was defined as FCP < 250 µg/g (25).

Statistical analysis

Categorical data are shown as absolute numbers and percentages, whereas continuous variables are expressed as median values and measures of variability as interquartile ranges (IQR). Continuous variables were tested using the Mann-Whitney *U* test and categorical variables were analyzed using the Fisher's exact test. Univariate regression analysis was performed to identify factors associated with achieving target ITL in the induction phase.

Receiver operating characteristic (ROC) curves were used (1) to estimate the cut-off of the elimination half-life to achieve ITL > 3 µg/mL in the steady state and (2) to assess the discriminative ability of ITL to predict clinical remission and response and biochemical remission. For scoring purposes, a cut-off was chosen that would maximize the sum of sensitivity and specificity. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS for Windows (version 23.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Study population characteristics

The demographic and clinical characteristics of the 30 studied patients are shown in Table 1; 60.0 % (18 patients) were male, the median age was 40 (IQR: 26) and most patients had CD (22 patients; 73.3 %). Twenty-one patients (70.0 %) were taking a concomitant immunosuppressant, the most frequent was azathioprine (18 patients; 85.7 %) and ten patients (33.3 %) had been treated previously with a biological drug. Most patients were being treated with a infliximab biosimilar (25 patients; 83.3 %).

Pharmacokinetic variability of infliximab at week 6

Median ITL at week 6 during the induction period was 14.7 µg/mL (IQR: 12.8). Only 13 patients (43.3 %) had an ITL > 15 µg/mL, while 14 (46.7 %) had an ITL between 5-10 µg/mL, and three patients (10.0 %) had an ITL of < 5 µg/mL. No differences in the ITL were found between the diagnosis of CD and UC (14.8 µg/mL (IQR: 14.7) *vs* 14.0 µg/mL (IQR: 10.0), respectively; p = 0.45) nor between the ITL of the patients treated with infliximab originator (14.9 µg/mL [IQR: 11.2]) and infliximab biosimilar (14.7 µg/mL [IQR: 12.6]) (p = 0.416). No differences were found between naive patients and those previously treated with a biological drug (15.0 µg/mL [IQR: 14.2] *vs* 14.2 µg/mL [IQR: 9.0], respectively; p = 0.681).

The pharmacokinetic parameters obtained from the Bayesian prediction based on a population pharmacokinetic model for dose adjustment are shown in table 2. Individual predicted concentrations were within ± 1 and ± 1.5 µg/mL of the observed concentration for 50.0 % and 60.0 % of measurements, respectively. A cut-off point of the elimination

Table 1. *Baseline characteristics of patients*

	Total n = 30	CD n = 22	UC n = 8
Male, n (%)	18 (60.0)	14 (63.6)	4 (50.0)
Median age, (IQR) years	40 (26)	42 (31)	38 (19)
Weight, (IQR) Kg*	73.5 (27)	77 (19)	70 (29)
CD location, n (%)			
L1 (ileal)	-	6 (27.3)	-
L2 (colonic)	-	3 (13.6)	-
L3 (ileocolonic)	-	12 (54.5)	-
Others	-	1 (4.5)	-
CD behavior, n (%)			
B1 (nonstricturing, nonpenetrating)	-	6 (27.3)	-
B2 (stricturing)	-	11 (50.0)	-
B3 (penetrating)	-	5 (22.7)	-
Perianal disease, n (%)	-	8 (36.4)	-
UC location, n (%)			
E1 (proctitis)	-	-	1 (12.5)
E2 (left-sided colitis)	-	-	1 (12.5)
E3 (pancolitis)	-	-	6 (75.0)
Previous biological therapy, n (%)	10 (33.3)	7 (31.8)	3 (37.5)
Previous steroidal therapy, n (%)	17 (56.7)	10 (45.5)	7 (87.5)
Concomitant immunomodulator, n (%)	21 (70.0)	15 (68.2)	6 (75.0)
Biosimilar IFX, n (%)	25 (83.3)	18 (81.8)	7 (87.5)
Biochemical parameters, median (IQR)			
Albumin, g/dL	4.1 (0.3)	4.1 (0.3)	4.3 (1)
FCP, µg/g	1232.0 (1408.5)	1043 (1266)	1645.5 (1403.8)
CRP, mg/L	0.4 (0.65)	0.4 (0.6)	0.4 (3.3)
Clinical score at time of infusion, median (IQR)			
HBI	-	6.5 (6.0)	-
Partial Mayo	-	-	9.0 (1)

CD: Crohn's disease; UC: ulcerative disease; TNF: tumor necrosis factor; IFX: infliximab; FCP: calprotectin; CRP: C-reactive protein; HBI: Harvey Bradshaw Index.

Table 2. *Estimated pharmacokinetic parameters according to infliximab trough levels at week 6 of induction period*

	ITL < 15 µg/mL	ITL > 15 µg/mL	*p* value
Cmin, µg/mL	9.5 (8.0)	20.6 (3.5)	< 0.001
IPRED, µg/mL	10.5 (6.6)	21.1 (5.3)	< 0.001
K_{el}, h^{-1}	0.005 (0.001)	0.003 (0.001)	0.003
Vc, L	3.416 (0.427)	4.080 (0.322)	< 0.001
Vp, L	1.206 (0.212)	1.3450 (0.227)	0.025
Cl, $L \cdot h^{-1}$	0.015 (0.005)	0.014 (0.003)	1.000
$T_{1/2}$, h	154.360 (38.062)	206.250 (33.778)	0.003

ITL: infliximab trough levels; Cmin: minimum observed concentration; IPRED: individual model-predicted concentrations; Kel: elimination-rate constant; Vc: central distribution volume; Vp: peripheral distribution volume; Cl: clearance; T1/2: elimination half-life.

half-life of 194.2 h predicted the achievement of a steady state ITL > 3 µg/mL, with a sensitivity of 100 % and a specificity of 95.5 % (AUC: 0.994 [CI 95 %: 0.976-1.0; p < 0.001]).

Factors associated with achieving ITL > 15 µg/mL at week 6

The results of the univariate analysis (Table 3) showed that the only factor associated with achieving ITL > 15 µg/mL was body weight; for an increase of 1 kg in body weight (OR: 1.105 [95 % CI: 1.021-1.196]). The other variables studied (age, sex, diagnosis of CD, perianal disease, biosimilar infliximab, FCP, albumin, CRP, previous biological drug therapy, previous steroidal therapy and concomitant immunosuppressive) were not associated with achieving greater levels.

Table. *3 Univariate analysis of the associated factors for achieving infliximab trough levels > 15 µg/mL at week 6 of the induction period*

	Univariate analysis OR (95 % CI), p value
Male sex	1.120 (0.256-4.905), 0.880
Age, years	1.050 (0.997-1.106), 0.067
Diagnosis Crohn	1.389 (0.264-7.299), 0.698
Weight, kg	1.105 (1.021-1.196), 0.013
Perianal disease	0.692 (0.136-3.518), 0.658
Biosimilar IFX	0.85 (0.120-5.998), 0.467
FCP, µg/g	1.000 (0.999-1.001), 0.552
Albumin, g/dL	3.331 (0.517-21.440), 0.205
CRP, mg/L	0.900 (0.490-1.651), 0.733
Previous anti-TNF therapy	0.429 (0.086-2.148), 0.303
Concomitant immunosuppressive	1.067 (0.221-5.145), 0.936
Previous steroidal therapy	0.260 (0.56-1.201), 0.085

IFX: infliximab; FCP: calprotectin; CRP: C-reactive protein; TNF: tumour necrosis factor.

Post-induction dosing strategy according to the Bayesian prediction model

Half of the patients received intensified therapy after week 6 of the induction period. Interval reduction was performed (5 mg/kg every 4, 5 or 6 weeks) in ten (33.3 %) patients. The interval was reduced and the dose was increased (7.5 mg/kg every 4, 5 or 6 weeks and 10 mg/kg every 4 weeks) in four (13.3 %) patients and the dose was increased to 10 mg/kg every 8 weeks in one patient (3.3 %).

Clinical and biochemical response at week 26

Of the total patients included, two discontinued the therapy before the end of the 6-month period due to adverse reactions to drugs. The median ITL in the maintenance period was 5.2 µg/mL [IQR: 5.9]. Twenty-three (82.1 %) patients had therapeutic ITLs in the range 3-10 µg/mL and 15 (53.6 %) patients achieved levels over 5 µg/mL. Of the 15 patients who received intensified therapy post-induction, 11 (73.3 %) achieved the target therapeutic range at week 26 of treatment. No statistically significant differences were found between the intensified and non-intensified group achieving ITL (6.3 µg/mL [12.9] *vs* 4.4 µg/mL [4.1], p = 0.185), clinical response (78.6 % *vs* 69.2 %, p = 0.580), biochemical remission (61.5 % *vs* 46.7 %, p = 0.431) and clinical remission (64.3 % *vs* 76.9 %, p = 0.472). Two patients discontinued treatment due to the presence of ATI (686.0 and 30.6 AU/mL).

A clinical response was observed in 71.4 % of patients, whose ITLs were significantly higher than in the non-responders (6.3 µg/mL [IQR: 6.7] *vs* 1.0 µg/mL [IQR: 5.0], respectively; p = 0.016). The AUC for predicting clinical response by means of ITL was 0.804 [CI 95 %: 0.616-0.991] (p = 0.019), with a sensitivity of 70 %, specificity of 71.4 % and a cut-off of 4.43 µg/mL. In addition, 53.6 % of patients achieved biochemical remission, levels were higher in this group than in non-responders (6.2 µg/mL [IQR: 5.2] *vs* 3.2 µg/mL [IQR: 5.0], respectively; p = 0.031). The AUC for predicting biochemical remission by means of ITL was 0.750 [CI 95 %: 0.550-0.950] (p = 0.031), with a cut-off point of 4.53 µg/mL for predicting responses (Se 71.4 % and Sp 75.0 %). A reduction of more than half of the basal FCP was also noted in 63.3 % of patients. However, no significant statistical differences were observed between ITL at week 26 and clinical remission (p = 0.481), for which the AUC only had low statistical power (AUC: 0.592 [CI 95 %: 0.324-0.861]; p = 0.481). The details of these analyses are shown according to diagnosis in figure 1.

DISCUSSION

Primary non-response to infliximab therapy occurs in around 30 % of IBD patients (4,5,26). Pharmacokinetic processes associated with inadequate drug exposure and/or the development of anti-drug antibodies could play a key role in this finding (9,10). The main objectives of our study were to evaluate the pharmacokinetic variability of infliximab and to determine the factors associated with achieving optimal ITL in the induction phase. We observed that less than half of patients had the target ITL (> 15 µg/mL) at week 6 of the induction period. Furthermore, we analyzed the relationship between ITL and the clinical and biochemical response at week 26 of treatment.

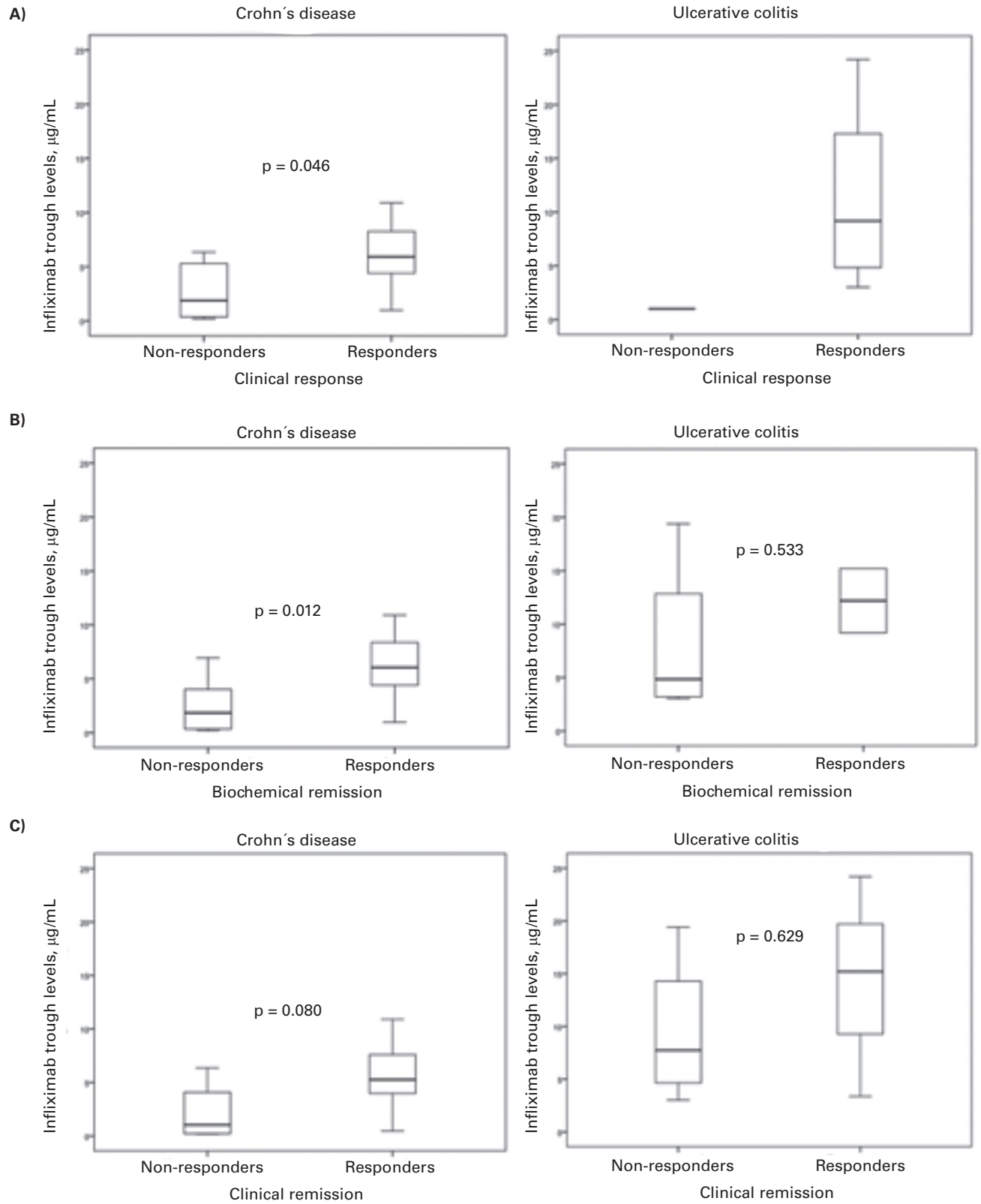

Fig. 1. *Association of infliximab trough levels (µg/mL) with (A) clinical response, (B) biochemical remission and (C) clinical remission at week 26. Box plots show comparison of median infliximab maintenance levels between non-responders and responders, according to diagnosis.*

Although well-designed large prospective studies are lacking, several observational recent studies have shown that higher ITLs are associated with favorable short-term and long-term therapeutic outcomes in IBD (27-30). However, to our knowledge, no previous studies have determined the percentage of patients that achieve a therapeutic ITL in the induction phase. For example, Kobayashi et al. (27) have shown that trough level at week 2 is significantly associated

with 14-week clinical remission. A study by Papamichael et al. (17) in a cohort of 101 patients with UC showed that higher infliximab concentrations during induction therapy were associated with short-term mucosal healing. Davidov et al. (15) also demonstrated that high ITLs at weeks 2 and 6 were associated with fistula response at weeks 14 and 30.

Different studies have demonstrated that the main risk factors for increased clearance of infliximab are the presence of ATI, a high inflammatory burden (elevated CRP, low albumin and loss of drug through stool), infliximab monotherapy and body weight (11,31). In a retrospective observational case-control study of IBD patients, Bar-Yoseph et al. (26) demonstrated that an ITL below 6.8 µg/mL and ATI levels above 4.3 µg/mL before the second infusion were associated with primary non-response. Beltran et al. (5) showed that a high inflammatory burden (measured with CRP and FCP levels) can impact on the clinical response to infliximab due to accelerated clearance of the drug. In our study, body weight was the only variable associated with an increased likelihood of optimal ITL. This is concordant with other studies that suggest that it could be explained by weight-based dosing (11,31). Dotan et al. (31) showed that patients with a lower body weight (e.g., 40 kg) were expected to have a 35 % lower drug exposure than an 80 kg patient given the same 5 mg/kg standard dose. This ultimately results in lower trough concentrations at the end of the dose interval.

We believe that the induction phase is probably an ideal stage at which to measure serum drug concentrations, since decisions must be taken as soon as possible (16). Early optimization of biological therapy based on proactive TDM could provide benefits in clinical and pharmacokinetic outcomes, quality of life and pharmacoeconomics (21). Clinical pharmacists play an important role in ensuring appropriate clinical pharmacokinetics and cost-effective TDM assessments. We feel that it is worth emphasizing we observed in our study that patients with an elimination half-life below 194.2 h were more likely not to achieve therapeutic levels in the maintenance phase (once the steady state was achieved). Therefore, the steady-state concentration should not be the only indicator for optimizing treatment in these patients. The development of individualized dose regimens should be based on findings from monitoring of both the drug concentration-*vs*-time profiles in biological fluids and the pharmacological responses to these drugs (32). We consider that applying the population pharmacokinetic model with a Bayesian prediction model approach represents a significant step forward in optimizing infliximab dosing in the management of IBD and may make individualized therapy possible (33). Further prospective studies and validation in large populations will help determine the optimal role of pharmacokinetic models during the induction phase, for posology adjustments in biological therapies in patients with IBD.

Dose adjustment after induction was performed by a multidisciplinary team based on a Bayesian pharmacokinetic model and clinical criteria. In our study, half of the patients received intensified therapy after week 6 and 82.1 % of all patients achieved a therapeutic ITL of 3.0-10.0 µg/mL in the maintenance phase (4). A recent study (34) has shown that proactive TDM is associated with fewer surgeries and higher rates of mucosal healing than conventional non-TDM-based management and can prevent primary non-response.

Our findings are consistent with those of other studies such as Papamichael et al. (4), who have developed a consensus regarding the use of TDM as biologic therapy in IBD. During maintenance, the trough concentration of infliximab for patients in remission should be over 3 mg/mL, whereas for mucosal healing and perianal disease the ITL should be higher, > 5 and > 10 µ/mL, respectively (23,35).

Our study had several limitations. First, despite the retrospective nature of the study, the data collected for the TDM were obtained prospectively, which reduced the amount of missing data. Second, due to the small sample size, it was not possible to obtain significance in some outcomes and subgroup analysis. However, we observed a positive association between ITL and clinical response and biochemical remission at week 26. Third, the lack of fecal calprotectin data and activity indices at the end of induction did not allow us to assess whether early proactive TDM prevents primary non-response. In addition, it would have been interesting to have a control group to detect differences with the pharmacokinetic outcomes after dose intensification. However, our findings are consistent with a TAXIT study performed by Vande Casteele et al., who showed that the proactive TDM of infliximab compared to clinically based dosing is associated with a lower frequency of undetectable drug concentrations and a lower risk of relapse (7).

To our knowledge, there are few studies that have determined the pharmacokinetic variability of ITL in the induction phase by estimating individual pharmacokinetic parameters. We consider the characterization of our patients from a pharmacokinetic point of view to ensure adequate exposure to the added value. The inclusion of population pharmacokinetic models with Bayesian estimations in the decision making can be a useful strategy for individualized dose regimens (20).

In summary, we have shown that less than half of patients had target ITL in the induction period. TDM during this period was related to the achievement of therapeutic levels of infliximab and may lead to a better clinical response in patients with IBD. However, prospective studies are needed to examine the usefulness of proactive TDM in the induction phase. Likewise, the presence of clinical pharmacists in a multidisciplinary team can improve the treatment of patients with IBD.

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