Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 5 Issue 10 October 2022

Research Article

Are Sufficient Induction Dose of Anti-TNF Drug for Avoid Failure Pharmacokinetic in Patients with Inflammatory Bowel Disease? A Study in a Real World Setting

Carles Iniesta Navalón[1]*, Lidia Díaz Serrano[2], Lorena Rentero Redondo[1], María Ángeles Nieto Vitoria[2], Consolación Pastor Mondéjar[1], Rosa Gómez Espín[2] and Isabel Nicolás De Prado[2]

[1]PhD, Department of Hospital Pharmacy, Reina Sofia Hospital of Murcia, Spain

[2]MD, Department of Gastroenterology, Reina Sofia Hospital of Murcia, Spain

***Corresponding Author:** Carles Iniesta Navalón, PhD, Department of Hospital Pharmacy, Reina Sofia Hospital of Murcia, Spain.

Received: September 14, 2022

Published: September 28, 2022

© All rights are reserved by **Carles Iniesta Navalón.*, et al.***

Abstract

Objectives: Pharmacokinetic processes associated increased drug clearance could play a key role in primary no-responders to anti-TNF drug in inflammatory bowel disease patients. To our knowledge, little is known about whether drug exposures after induction doses are sufficient to avoid pharmacokinetic failure in real life. The main objective of this study was to determine the proportion of patient adalimumab and infliximab-treated, with pharmacokinetic failure at induction period, and to investigate the factors associated with increase clearance.

Methods: We conducted a retrospective observational study. Patients starting treatment with adalimumab or infliximab during May 2017 to June 2021 were potentially eligible for the study. The primary outcome was to determine the proportion of patients with drug concentration at induction period, and to investigate baseline patient-related characteristics affecting to drug elimination. Individual pharmacokinetic parameters were estimate by Bayesian method for each patient.

Results: A total of 101 patients were included in the study. The proportion of patients with serum concentrations in the therapeutic range was higher in patients treated with adalimumab than infliximab (74.5% vs. 40.0%, respectively; $p < 0.001$). After multivariate analysis, the factors associated with a short half-life (<163 hours) for infliximab were: diagnosis UC (OR: 5.62 [CI95% 1.01 -32.5]), serum albumin (OR: 0.26 [CI 95%: 0.03 - 0.90]), and anti-TNF-α previous treatment (OR: 8.86 [CI 95%: 1.10-71.48]).No association were found for ADA.

Conclusion: The findings of this study justify the early measurement of drug levels to be able to optimize therapy appropriately and avoid lack of response, especially in patients at risk.

Keywords: Infliximab; Adalimumab; Therapeutic Drug Monitoring; Induction; Inflammatory Bowel Disease; Pharmacokinetic

Introduction

Primary non-response (PNR) to anti-TNF therapy occurs in around 10-40% of IBD patients [1-3]. PNR is usually defined as non-response by the end of induction and may be for pharmacokinetic or pharmacodynamics reasons. Pharmacokinetic PNR is due to increased drug clearance, which may be immune mediated or non-immune mediated. Pharmacodynamics PNR occurs when active disease persists despite therapeutic biologic drug levels [4,5].

Therapeutic drug monitoring (TDM) is a tool that allows the individual optimization of dosage regimens of drugs with high in-

ter-individual variability, to ensure adequate exposure to the drug [6-8]. 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 [9]. Early identification of patients with low anti-TNF levels and presence of immunogenicity may help to predictor patients at greater risk for treatment failure. Several studies show that there is considerable variability in trough levels of infliximab in the induction phase [4,5,10-12]. This initial phase is characterized by active disease (often characterized by low serum albumin), with a higher inflammatory load, and sometimes, with loss of drug through the stool leading to higher drug clearance and lower serum anti-TNF drug concentrations [11,13-16].

To our knowledge, little is known about whether drug exposures after induction doses are sufficient to avoid pharmacokinetic failure in a real-world setting. Therefore, the main objective of this study was to determine the proportion of patient adalimumab and infliximab-treated with pharmacokinetic failure at end of period induction, and to investigate the factors associated with increase clearance. Secondarily, we study dose management according to drug levels in the induction phase.

Methods

We conducted a retrospective observational study in a hospital in Murcia (SE Spain), which provides medical care to 200,892 patients. Patients starting treatment with adalimumab (ADA) or infliximab (IFX) during May 2017 to June 2021 were potentially eligible for the study. The inclusion criteria were outpatients with IBD, age > 16 years, who had received an induction dose for IFX of 5 mg/kg at 0, 2 and 6 weeks or ADA loading dose of 160 mg and 80 mg subcutaneously at week 0 and week 2, respectively, followed by a maintenance dose of 40 mg subcutaneously every other week. Patients without serum concentration at the end of the induction period of ADA (week 4) and IFX (week 6) or those without information relating to their clinical responses or laboratory parameters were excluded. The study was approved by the local research ethics committee.

Variables

Demographic and clinical variables collected, at the time of ADA or IFX start, included gender, age, body weight, diagnosis, disease behavior and location according to the Montreal Classification at diagnosis [17], perianal disease, previous biological, the use of concomitant immunosuppressive therapy, biosimilar infliximab or adalimumab treatment, serum albumin, and faecal calprotectin. Also, data from endoscopic assessment (UCEIS index for UC and SES-CD for CD patients) performed at least three months prior to the start of anti-TNF treatment were collected. Severe endoscopic activity was considered when UCEIS index≥6 and SES-CD≥16.

ADA and IFX concentrations were determined from serum samples collected prior to administration at week 4 or 6, respectively (induction period). The data about serum drug concentration were obtained from a local database of the Clinical Pharmacokinetics Unit (Department of Pharmacy). Serum trough levels and antibodies to ADA and IFX were measured using an available validated enzyme-linked immunosorbent assay (ELISA) kit (PromonitorR; Grifols, Spain).

Outcomes

The primary outcome was to determine the proportion of patients with ADA/IFX trough concentration at induction period, and to investigate baseline patient-related characteristics affecting to drug elimination (half-life elimination). For this, the individual pharmacokinetic parameters were estimate by Bayesian method for each patient, using NONMEM software version 7.3 based on the population pharmacokinetic for ADA [18] and IFX [19]. Trough levels ADA ≥ 8 μg/mL and IFX≥ 15 μg/mL at induction period were considered optimal [4,5,20].

The secondary outcome was to analyze the proportion of patients with trough concentrations in therapeutic range in six month after the dose management according trough levels obtained in the induction period. Adalimumab trough concentration >5 μg/mL, and IFX TC as ≥ 3 μg/mL and as ≥ 5 μg/mL ml were considered as the optimal cut-off values in CD and UC, respectively [7,20]. The dosage regimen was optimized in each patient according to the trough levels, symptoms and biochemical parameters.

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. Receiver operating characteristic (ROC) curves were used to estimate the cut-off of the half-life elimination of ADA and IFX in pa-

tients with trough concentration optimal in induction period. The best cut-off value was generated according to the maximal value of sensitivity plus specificity. Multivariate logistic regression (step forward procedure) was used in order to identify associated factors with an increased clearance, including those factors previously defined as statistically significant according to the univariate regression analysis. 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).

Ethical considerations

The study was approved by the local research ethics committee.

Results

A total of 101 patients were included in the study, 50 received treatment with IFX and 51 with ADA. Sixty-four (63.4%) were male 63.4%; the median age at start anti-TNF treatment was 41.8 years [IQR: 15.3]. Seventy-one patients (70.3%) had Crohn´s disease (CD), and thirty (29.7%) had ulcerative colitis (UC). Seventy-eight (77.2%) patients had not received prior biological treatment. The baseline characteristics of the study population are shown in table 1.

Serum concentration at induction period

The proportion of patients with serum concentrations in the therapeutic range in induction period was higher in patients treated with ADA than with IFX (74.5% vs. 40.0%, respectively; p<0.001). Median ADA concentration at week 4 of induction was 10.4 µg/mL [IQR: 4.4], and six patients (11.8%) had ADA concentration below 5 µg/mL (Figure 1A). Median IFX concentration at week 6 of induction was 13.5 µg/mL [IQR: 12.9], and 11 patients (22.0%) had IFX concentration below 5 µg/mL. No differences were found between the diagnosis of CD and UC (Figure 1B).

	Infliximab (n = 50)	Adalimumab (n = 51)	Total (n = 101)	p
Male, n (%)	30 (60.0)	34 (66.7)	64 (63.4)	0.487
Age at start of IFX, mean (SD)	43.5 (15.5)	41.0 (15.3)	41.8 (15.3)	0.820
UC, n (%)	19 (38)	11 (21.6)	30 (29.7)	0.071
UC location, n (%)				
E1 (proctitis)	1 (5.3)	0	1 (3.3)	0.439
E2 (left-sided colitis)	5 (26.3)	4 (36.4)	9 (30.0)	0.563
E3 (pancolitis)	13 (68.4)	7 (63.6)	20 (66.7)	0.789
CD, n (%)	31 (62.0)	40 (78.4)	71 (70.3)	0.071
CD location, n (%)				
L1 (ileal)	12 (38.7)	15 (37.5)	27 (38.0)	0.917
L2 (colonic)	4 (12.9)	4 (10.0)	8 (11.3)	0.701
L3 (ileocolonic)	15 (48.4)	21 (52.5)	36 (50.7)	0.731
CD behaviour, n (%)				
B1 (nonstricturing, nonpenetrating)	7 (22.6)	17 (42.8)	24 (33.8)	0.078
B2 (stricturing)	17 (54.8)	10 (25.0)	27 (38.0)	0.01
B3 (penetrating)	7 (22.6)	13 (32.5)	20 (28.2)	0.357
Perianal disease, n (%)	6 (12.)	10 (19.6)	16 (15.8)	0.295
Biosimilar IFX, n (%)	45 (90)	45 (88.2)	90 (89.1)	0.776
Anti-TNF therapy previous	13 (26.0)	10 (19.6)	23 (22.8)	0.444
Immunosuppressive concomitant, n (%)	33 (66.0)	36 (70.6)	69 (68.3)	0.620

Table 1: Characteristics population study (n = 104).

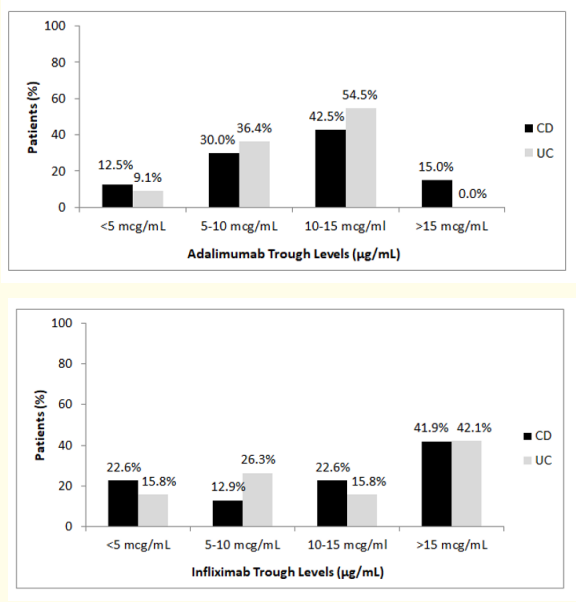

Figure 1: Distribution of adalimumab (1A) and adalimumab (1B) trough levels according to different ranges in induction, with an arbitrary subdivision in 5 ranges of IFX serum values (<5 µg/mL, between 5-10 µg/mL, between 10-15 µg/mL,15-20 µg/mL >20 µg/mL). CD: Crohn Disease, UC: Ulcerative Colitis.

Regarding immunogenicity during the induction period, three cases were observed (two IFX and one ADA).

Factors associated with increased anti-TNF drug clearance

Table 2 summarizes the estimated pharmacokinetic parameters of adalimumab and infliximab, in patients with and without optimal drug concentrations at induction period. For IFX a cut-off point of the elimination half-life of 163 hours predicted IFX concentration ≥15 µg/mL at week 6, with a sensitivity of 85% and specificity of 76.7% (AUC: 85.7% [CI 95%:74.9% - 96.4%], $p < 0.001$). After performing the multivariate analysis, the factors associated with a short half-life (<163 hours) for IFX were: diagnosis UC (OR: 5.62 [CI95% 1.01 -32.5]), serum albumin (OR: 0.26 [CI 95%: 0.03 - 0.90]), and anti-TNF previous treatment (OR: 8.86 [CI 95%: 1.10-71.48]). For ADA a cut-off point of the elimination half-life of 506 hours predicted ADA concentration ≥ 8 µg/mL at week 4, with a sensitivity of 96.6% and specificity of 100% (AUC: 100%, $p < 0.001$). Unlike IFX, no association was found between the short half-life (<506 hours) and the variables studied (Table 3).

A subgroup analysis was performed, including patients with CD with colon involvement and with a diagnosis of UC, to analyze the association between baseline calprotectin and increased drug clearance. It was observed that patients with basal calpro-

	Adalimumab			Infliximab		
	<8 µg/mL	**≥8 µg/mL**	**p**	**<15 µg/mL**	**≥15 µg/mL**	**p**
Cmin, µg/mL	5.2 (5.9)	13.6 (3.2)	<0.001	6.8 (9.2)	19.6 (4.5)	<0.001
IPRED, µg/mL	6.0 (4.2)	10.8 (3.2)	<0.001	8.9 (7.7)	21.5 (7.2)	<0.001
Vc, L	13.6 (2.4)	11.9 (2.3)	0.005	3.5 (0.3)	3.9 (0.7)	0.049
Vp, L				1.1 (0.2)	1.4 (0.3)	<0.001
Cl, $L \cdot h^{-1}$	0.03 (0.02)	0.012 (0.005)	<0.001	0.017 (0.008)	0.014 (0.003)	0.07
$T_{1/2}$, h	350.8 (275.8)	642.6 (115.3)	<0.001	144.0 (49.7)	197.6 (54.4)	<0.001
K_{el}, h^{-1}	0.002 (0.002)	0.001 (0.0002)	<0.001	0.005 (0.002)	0.0041 (0.001)	<0.001

Table 2: Estimated pharmacokinetic parameters according to Infliximab (week 6) and adalimumab (week4) Trough Levels at induction period.

Cmin: Minimum Observed Concentration; IPRED: Individual Predicted Concentrations; Vc: Central Distribution Volume; Vp: Peripheral Distribution Volume; Cl: Clearance; T1/2: Elimination Half-life; Kel: Elimination-Rate Constant.

	Infliximab		Adalimumab	
	Univariant	Multivariant	Univariant	Multivariant
Albumin	0.24 (0.10 - 0.92)	0.26 (0.03 - 0.90)	0.16 (0.02 - 1.40)	-
Calprotectin > 500 µg/g	3.84 (1.04 - 14.21)	-	0.58 (0.08 - 4.01)	-
Ulcerative colitis	9.70 (2.31 - 40.80)	5.62 (1.01 - 31.50)	1.125 (0.25 - 5.10)	-
Perianal disease	0.29 (0.05 - 1.65)	-	0.586 (0.11 - 3.15)	-
Female gender	0.94 (0.30 - 2.91)	-	3.587 (0.70 - 18.51)	-
Age at start treatment	1.00 (0.97 - 1.04)	-	1.03 (0.99 - 1.08)	-
Anti-TNF previous	6.15 (1.44 - 26.40)	8.86 (1.10 -71.467)	0.753 (0.16 - 3.47)	-
Weight, Kg	0.97 (0.93 - 1.01)	-	1.01 (0.95 - 1.07)	-
Severe endoscopic activity	1.44 (0.26 -8.03)	-	0.365 (0.04 - 3.89)	-

Table 3: Univariate and multivariate analysis for factors associated with the presence of increased anti-TNF drug clearance. Increased drug clearance was considered when the cut-off point after the ROC curve analysis was 506h and 163h for adalimumab and infliximab, respectively. Severe endoscopic activity was considered when UCEIS index≥6 and SES-CD≥16.

tectin>500 µg/g had a higher clearance in the case of IFX (OR: 7.0 [CI95%: 1.39 - 35.34]), but not in the case of ADA.

Dose management according to ADA and IFX concentrations in induction period

In most patients (86.8%) with ADA trough concentrations optimal at week 4, no dose adaptation was performed. Of these, 84.6% reached through levels ≥5 µg/mL in the maintenance phase. In the subgroup of patients with infratherapeutic levels of ADA (<8 µg/mL) in the induction phase, dose intensification was performed in 76.9%, of which 90% achieved optimal concentrations after dose escalation (Figure 2A). No case of immunogenicity against adalimumab was detected in the following measure of serum levels

In the group of patients with IFX levels in the therapeutic range at week 6, the standard regimen (5 mg/kg/8 weeks) was maintained in 90% of cases. Of these, 78.6% reached optimal concentrations in the maintenance phase. Similar results (76.9%) were observed in the subgroup of patients intensified due to infra-therapeutic IFX levels in the induction period. Unlike adalimumab, two patients with anti-IFX antibodies were detected despite dose escalation (Figure 2B).

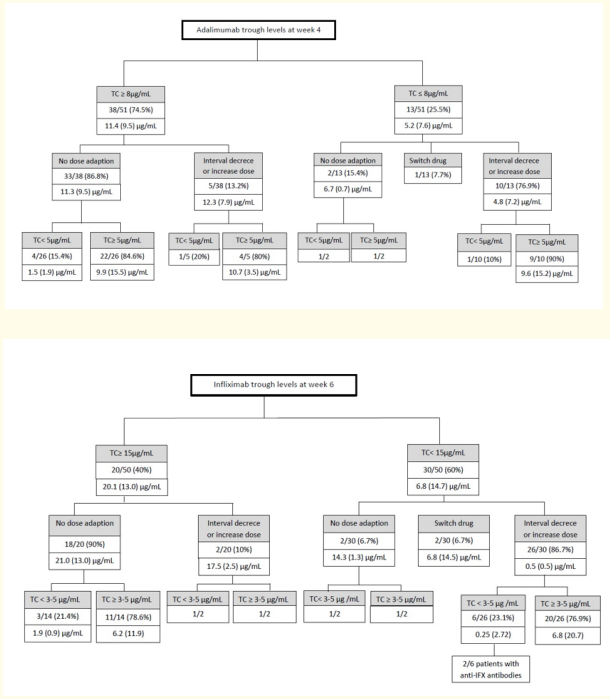

Figure 2: Dose management according to adalimumab (2A) and infliximab (2B) trough levels at induction period. Infliximab trough level X TC as ≥ 3 µg/mL and as ≥ 5 µg/mL ml were considered as the optimal cut-off values in CD and UC, respectively, in maintenance period.

Discussion and Conclusion

Pharmacokinetic processes associated increased drug clearance, could play a key role in primary no-responders [1-3]. The

main objective of this study was to determine the proportion of patient with pharmacokinetic failure at end of period induction, and to investigate the factors associated with increase clearance. We observed that less than half of the patients (40%) IFX-treated achieved optimal concentrations at end of induction period, while in the case of patients ADA-treated the rate was higher (75%).

Early identification of patients with low anti-TNF-α levels and presence of immunogenicity may help to predictor patients at greater risk for treatment failure. We considered that TDM in phase of induction is of particular importance because patients with active disease typically have a significant inflammatory burden and loss of drug through stool leading to higher drug clearance and lower serum anti-TNF drug concentrations predisposing also to the development of antidrug antibodies [20-22]. In line with previous studies [4,5,15,16], we observed that, the factors independently associated with increased IFX clearance were the diagnosis of ulcerative colitis, low basal albumin, and previous treatment with anti-TNF. Biomarkers, such as faecal calprotectin, have been reported to be strongly correlated with clinical remission and mucosal healing during therapy with IFX and ADA [15,23]. In our study, we shown an association between high baseline calprotectin (>500 µg/g) and increased IFX clearance, especially, in patients with colonic affectation of IBD. Higher body weight has been correlated with greater drug clearance in pharmacokinetics studies. However, this association is nonlinear, while drug dosing in based on linear relationship. Therefore, patients with low weight may have a greater risk of achieving low drug levels [16,19,24]. In contrast, no association was found for ADA, without having any explanation for this.

The therapeutic drug window for anti-TNF induction therapy remains still largely unknown. Verstockt., *et al*. [13], shown that patients with low serum levels of ADA at week 4 (<8.3 µg/mL) were at significantly higher risk of immunogenicity a short term, and increase the risk for adalimumab discontinuation. Other study conducted by Zittan., *et al*. [11], found that higher ADL trough levels at week 4 were significantly associated with clinical remission (13.9 µg/mL) and biological remission (16.2 µg/mL) at week 24. Papamichael., *et al*. [10] identified an adalimumab concentration ≥7.5 µg/ml at week 4 as factors independently associated with mucosal healing a short-therm. A study by Papamichael., *et al*. [25] in a cohort of 101 patients with UC showed that higher infliximab concentrations during induction therapy (≥15 µg/mL) were associated with short-term mucosal healing. Davidov., *et al*. [26] also demonstrated that high ITLs at weeks 2 and 6 were associated with fistula response at weeks 14 and 30. Finally, a recently consensus statements [20], based on interpretation of the available literature, established that, IFX (at week 6) and ADA (at week 4) trough concentrations should be at least 15-20 µg/mL and 8-12 µg/mL, respectively.

In our opinion, an appropriate timing to measurement levels of anti-TNF in induction phase should to be evaluated, especially, in patients with risk of increase clearance. Hypothetically, making the first determination in week 2, before administering the dose, may be advantageous to detect a low exposure to the drug, and consequently early dose optimisation, and use an intensive monitoring strategy to ensure adequate exposure of the drug. The availability of a point-of-care test for TDM might represent an important step forward for improving the management of IBD patients. These assays, unlike traditional ELISAs, provide a rapid assessment of drug concentrations and allow immediate drug dose adjustment.

On the other hand, we consider the implementation of population pharmacokinetic models in decision-making to be essential for optimal individualization [27-30]. In our study, we used pop-PK models to estimate individual pharmacokinetic parameters of adalimumab and infliximab. However, we consider that there is a long way to go, because the pK software used in our study was designed for research applications rather than for clinical use. Its use in the daily clinical practice is labor-intensive and beyond the capabilities of most clinical practices. More user-friendly PK software programs are needed for use in the clinical practice.

Our study presents some limitations. First, this was a retrospective study with a relatively small cohort. However, the authors wish to emphasize that the data collected for the TDM were obtained prospectively, which reduces the amount of missing data. Second, clinical outcomes at end of induction period were not determined since our study focused on pharmacokinetic outcomes at end of induction period. Furthermore, many studies have shown a positive correlation between ITLs and favourable therapeutic outcomes [8,10-12,25,26]. Third, baseline endoscopic activity data were only available in 59 patients, possibly this was the reason for not finding an association with low drug exposure in the induction phase.

Despite the limitations mentioned above, we consider our study interesting because therein our knowledge, are few cohort studies,

in real life, that determine the proportion of patients with suboptimal exposure at end of induction. Also, in our study we investigate the basal characteristics of patients with high risk of failure pharmacokinetic in real clinical setting.

In summary, in our study we found a considerable proportion of patients with low exposure to infliximab, and to a lesser extent, to adalimumab. These findings justify the early measurement of drug levels to be able to optimize therapy appropriately and avoid lack of response, especially in patients at risk of increase anti-TNF drug clearance (hypoalbuminemia, colonic involvement, elevated basal calprotectin and with previous failure to anti-TNF drug).

Funding

This paper is not funded.

Data Availability

No new data were generated or analysed in support of this research.

Acknowledgments

We express our sincere appreciation to Prof Juan José Gascón Cánovas for the statistical advice.

Bibliography

1. Hanauer SB., *et al*. "Human Anti-Tumor Necrosis Factor Monoclonal Antibody (Adalimumab) in Crohn's Disease: the CLASSIC-I Trial". *Gastroenterology* 130 (2006): 323-333.

2. Rutgeerts P., *et al*. "Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis". *The New England Journal of Medicine* 353 (2005): 2467-2476.

3. Colombel JF., *et al*. "Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial". *Gastroenterology* 132 (2007): 52-65.

4. Papamichael K., *et al*. "Therapeutic Drug Monitoring during Induction of Anti-Tumor Necrosis Factor Therapy in Inflammatory Bowel Disease: Defining a Therapeutic Drug Window". *Inflammatory Bowel Disease* 23 (2017): 1510-1515.

5. Sparrow MP., *et al*. "Therapeutic Drug Monitoring of Biologics during Induction to Prevent Primary Non-Response". *Journal of Crohn's and Colitis* 14 (2020): 543-556.

6. Frymoyer A., *et al*. "Infliximab dosing strategies and predicted trough exposure in children with Crohn disease". *Journal of Pediatric Gastroenterology and Nutrition* 62 (2016): 723-727.

7. Papamichael K., *et al*. "Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients With Inflammatory Bowel Diseases". *Clinical Gastroenterology and Hepatology* 17 (2019): 1655-1668.

8. Casteele N Vande., *et al*. "Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease". *Gastroenterology* 148 (2015): 1320-1329.

9. Candel MG., *et al*. "Usefulness of therapeutic drug monitoring of infliximab during the induction period in patients with inflammatory bowel disease ORIGINAL PAPERS". R*evista Española de Enfermedades Digestivas* 112 (2020): 360-366.

10. Papamichael K., *et al*. "Post-induction adalimumab concentration is associated with short-term mucosal healing in patients with ulcerative colitis". *Journal of Crohn's and Colitis* 11 (2017): 53-59.

11. Zittan E., *et al*. "Post-Induction High Adalimumab Drug Levels Predict Biological Remission at Week 24 in Patients With Crohn's Disease". *Clinical and Translational Gastroenterology* 12 (2021): e00401.

12. Liefferinckx C., *et al*. "Infliximab Trough Levels at Induction to Predict Treatment Failure during Maintenance". *Inflammatory Bowel Disease* 23 (2017): 1371-1381.

13. Verstockt B., *et al*. "Influence of early adalimumab serum levels on immunogenicity and long-term outcome of anti-TNF naive Crohn's disease patients: the usefulness of rapid testing". *Alimentary Pharmacology and Therapeutics* 48 (2018): 731-739.

14. Toyonaga T., *et al*. "Usefulness of fecal calprotectin for the early prediction of short-term outcomes of remission-induction treatments in ulcerative colitis in comparison with two-item patient-reported outcome". *PLoS One* 12 (2017).

15. Kennedy NA., *et al*. "Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study". *Lancet Gastroenterology and Hepatology* 4 (2019): 341-353.

16. Naviglio S., *et al*. "How to predict response to anti-tumour necrosis factor agents in inflammatory bowel disease". *Expert Review of Gastroenterology and Hepatology* 12 (2018): 797-810.

17. Satsangi J., *et al*. "The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications". *Gut* 55 (2006): 749-753.

18. Ternant D., *et al*. "Pharmacokinetics of adalimumab in Crohn's disease". *European Journal of Clinical Pharmacology* 71 (2015): 1155-1157.

19. Adedokun OJ., *et al*. "Pharmacokinetics and Exposure Response Relationships of Ustekinumab in Patients With Crohn's Disease". *Gastroenterology* 154 (2018): 1660-1671.

20. Cheifetz AS., *et al*. "A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease". *American Journal of Gastroenterology* 116 (2021): 2014-2025.

21. Papamichael K., *et al*. "Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: Evolution in the definition and management of primary nonresponse". *Inflammatory Bowel Disease* 21 (2015): 182-197.

22. Brandse JF., *et al*. "Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis". *Gastroenterology* 149 (2015): 350-355.

23. Bertani L., *et al*. "Fecal Calprotectin Predicts Mucosal Healing in Patients With Ulcerative Colitis Treated With Biological Therapies: A Prospective Study". *Clinical and Translational Gastroenterology* 11 (2020): e00174.

24. Dotan I., *et al*. "Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: A population pharmacokinetic study". *Inflammatory Bowel Disease* 20 (2014): 2247-2259.

25. Papamichael K., *et al*. "Infliximab Concentration Thresholds During Induction Therapy Are Associated With Short-term Mucosal Healing in Patients With Ulcerative Colitis". *Clinical Gastroenterology and Hepatology* 14 (2016): 543-549.

26. Davidov Y., *et al*. "Association of Induction Infliximab Levels With Clinical Response in Perianal Crohn's Disease". *Journal of Crohns Colitis* 11 (2017): 549-555.

27. Gil Candel M., *et al*. "Usefulness of population pharmacokinetics to optimize the dosage regimen of infliximab in inflammatory bowel disease patients". *Revista Espanola de enfermedades* 112 (2020): 590-597.

28. Strik AS., *et al*. "Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial". *Scandinavian Journal of Gastroenterology* 56 (2021): 145-154.

29. Frymoyer A., *et al*. "Application of Population Pharmacokinetic Modeling for Individualized Infliximab Dosing Strategies in Crohn Disease". *Journal of Pediatric Gastroenterology and Nutrition* 65 (2017): 639-645.

30. Dubinsky MC., *et al*. "Dashboard-Driven Accelerated Infliximab Induction Dosing Increases Infliximab Durability and Reduces Immunogenicity". *Inflammatory Bowel Disease* (2022).