Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Manoel Alvaro de Freitas Lins Neto[1] João Otávio Moraes Rolim[1]
Diogo César Maurício de Oliveira Jatobá[2] Júnia Elisa Carvalho de Meira[1] Luís Henrique Salvador Filho[1]
Lucas Correia Lins[1] Jorge Artur Coelho Peçanha[1]

[1] Federal University of Alagoas, Universidade Federal de Alagoas Faculdade de Medicina, UFAL| UFAL FAMED, Maceió, Alagoas, Brazil
[2] Universidade Federal de Alagoas Faculdade de Medicina, UFAL FAMED, Maceió, Alagoas, Brazil

Address for correspondence Diogo César Maurício de Oliveira Jatobá, M.D, UFAL FAMED, Universidade Federal de Alagoas Faculdade de Medicina, Maceió, Alagoas, Brazil (e-mail: diogocesarm@hotmail.com).

J Coloproctol 2023;43(4): 276– 279.

Abstract

Inflammatory bowel disease (IBD) is a problem that directly affects the quality of life of patients suffering from this condition. Monitoring the serum level of infliximab (IFX) (TDM) is an important tool for guiding therapeutic decisions in IBD patients. The purpose of this study was to determine the significance of quantitatively measuring the serum level of IFX (TDM) and antibody to IFX (ATI). Methods and materials: Prospective observational study involving 40 IBD patients on IFX therapy, including 14 Proactive (week 06 of the induction phase) and 26 Reactive (maintenance phase). Immediately prior to the infusion, blood samples were drawn and measured using a Bulhlmann rapid test instrument. Serum concentrations of IFX were categorized as supratherapeutic (>7.0 micrograms/ml), therapeutic (between 3.0 and 7.0 micrograms/ml), and subtherapeutic (3.0 micrograms/ml). When the serum concentration of IFX was 3 mcg/ml (subtherapeutic), the ATI was measured. 25 patients with CD and 15 patients with UC were evaluated. Only three of the twenty patients with subtherapeutic serum levels had a positive ATI, and both were reactive; two had CD and one had UC. There was a statistically significant difference between reactive and proactive patients with respect to levels of CRP ($p = 0.042$), with proactive DNS patients suffering greater alterations in CRP and albumin.

Keywords
- infliximab antibody
- infliximab
- drug monitoring
- therapeutic drug

Introduction

Inflammatory bowel diseases (IBD) are chronic gastrointestinal (GI) pathologies caused by a dysregulation of the intestinal immune response. This pathology manifests itself in two ways: Crohn's disease (CD) and ulcerative colitis (UC). CD is distinguished by transmural GI tract involvement from the mouth to the anus. While UC only affects the colorectal mucosa. IBD is a public health problem that affects people of all ages and has a long course of disease that interferes with their quality of life by interfering with their social and productive lives.[1]

The therapeutic goal of IBD is not only symptom control, but also inflammatory control through agents that aid in

received
August 7, 2023
accepted after revision
October 24, 2023

DOI https://doi.org/10.1055/s-0043-1776892.
ISSN 2237-9363.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

mucosal healing and prevent irreversible structural injuries, thereby avoiding complications that can lead to hospitalization and surgery. It is well established that patients with IBD produce more tumor necrosis factor (TNF), a pro-inflammatory cytokine.[2] Immunobiological are medications that show a therapeutic response in the treatment of IBD at least on a regular basis. Anti-tumor necrosis factor (anti-TNF) is a type of biologic that is commonly used to treat CD and UC.

TDM in IBD is defined as the quantification of serum drug levels and/or antibody concentrations at a proper time point, which may guide the clinical assistant to take an appropriate action or dose adjustment during the treatment of a patient. In clinical practice, measuring serum levels of IFX immediately before infusion and antibodies to IFX (ATI) has been used to monitor response and guide treatment optimization or discontinuation in cases of loss of response to the drug, a strategy known as therapeutic drug monitoring (TDM).[3] This strategy appears to be a more cost-effective alternative to increasing the dose empirically, and it results in fewer episodes of disease relapse.[4] Proactive TDM is the therapeutic concentration of serum IFX following the induction dose (week 2 or/and week 6), whereas reactive TDM is the concentration during the maintenance phase.[5] The association of low serum IFX levels, the presence of ATI, high levels of C-reactive protein (CRP), high fecal calprotectin, and low levels of Albumin is one method of diagnosing loss of response.[6] Based on these assessments, IFX treatment can be continued or discontinued, and its dosage can be optimized between infusion doses or combined with an immunomodulator.[7] Our goal was to examine the quantitative measurement of IFX serum levels and the verification of the ATI, as well as its utility in the therapeutic management of infliximab patients.

Casuistic and Methods

An observational prospective cohort analysis was performed on 40 IBD patients at the Coloproctology Service of the Professor Alberto Antunes University Hospital (HUPAA) from August 2020 to January 2023. IFX was administered to 25 patients with Crohn's disease and 15 with UC. Blood samples were collected before the infusion of injectable immunobiologicals at the High Complexity Oncology Assistance Center (CACON) and at the Day Hospital. Serum-level analyses were conducted at the Institute of Multidisciplinary Skills in Intestinal Microbiota (InHaMMI) of the Faculty of Medicine (Famed) at the Federal University of Alagoas (UFAL).

Laboratory, endoscopic, imaging, and histological investigations confirmed the diagnosis of IBD in every patient. Everyone who participated signed the informed consent form, consenting to participate in the study and being free to opt out of the proposed research at any time.

Immediately prior to infusion, blood samples were collected for the measurement of serum levels of IFX and ATI. Being the measurement of the levels of IFX and ATI in InHaMMI using the Bulhlman reagent for a rapid test.

Before infusion, peripheral blood samples were centrifuged, and serum aliquots were frozen at -60°C. At the time of sample processing, frozen serum samples were thawed only once.

The lower limit of detection was 0.3 micrograms/ml. The therapeutic serum concentration of IFX was regarded as the determining factor for its upkeep. The presence of ATI was evaluated when the serum level was subtherapeutic and was either absent or high (> or equal to 8 micrograms/ml).[3]

All variables were descriptively analyzed using both absolute and relative frequencies. Fisher's Exact test was also used to determine statistically significant differences between patients whose serum levels were measured as Reactive versus Proactive for each study variable. All analyses utilized a significance level of P 0.05.

Results

Forty patients, 25 with CD and 15 with UC, 26 females and 14 males; 25 with CD and 15 with UC; 26 females and 14 males (►**Table 1**)

Six of the 14 patients who underwent proactive TDM had a subtherapeutic serum level (3 mcg/ml) and a negative ATI. 14 of the 26 patients with reactive MDD had subtherapeutic serum IFX (3 mcg), and the presence of ITA was investigated;

Table 1 Sample characterization by diagnosis

Variable	Crohn disease (n = 25)		Ulcerative colitis (n = 15)	
	N	%	n	%
Gender				
Male	8	32	6	40
Female	17	68	9	60
TDM				
Reactive	16	64	10	66,7
Proactive	9	36	5	33,3
Calprotectin				
Normal	10	40	4	26,7
Change	15	60	11	73,3
IFX				
Normal	4	16	2	13,3
Changed	21	84	13	86,7
AIT				
Positive	2	8	1	6,6
Negative	13	52	4	26,7
Not obtained	10	40	10	66,7
CRP				
Normal	15	60	11	73,3
Changed	10	40	4	26,7
Albumina				
Normal	19	86	11	73,3
Changed	6	24	4	26,7

however, only three patients, two with CD and one with UC, were positive for ATI.

In 26 patients, fecal calprotectin was altered (>200 milligrams), 15 had sub-therapeutic IFX serum levels, and two had positive ATI.

Ten patients had inadequate serum albumin (3.5), and eight had subtherapeutic IFX serum levels (3 mcg/ml) but no ATI. C-reactive protein (CRP) was altered in 14 patients, 10 of whom had subtherapeutic serum IFX, one of whom had a positive ATI, and four of whom had normal serum levels. 17 out of 20 patients with subtherapeutic IFX and a negative ATI were optimized. Only three patients relapsed 12 weeks after starting optimization with deteriorating biomarkers, requiring a change in the class of biologicals. There were three deaths: two patients with Crohn's disease (CD) and one with ulcerative colitis (UC) with sub-therapeutic IFX and positive ATI, and the biologic class was adjusted.

Two of the patients who were optimized and asymptomatic became pregnant, and the medication was discontinued at 30 weeks. Currently, ten patients are optimized and undergoing positive progression.

A supra-therapeutic dose was found in three patients with proactive MDD, a therapeutic dose in one, and a sub-therapeutic dose in four, all of whom were ATI negative. The four subtherapeutic MDD patients were subjected to optimization.

Nineteen patients had elevated serum IFX levels, while twenty-one had elevated fecal calprotectin (>200 micrograms/gram), CRP, and albumin levels within the normal range (3.5–5.2 grams per deciliter). In terms of CRP ($p = 0.027$) and albumin ($p = 0.013$), there was a statistically significant difference between proactive and reactive patients. More changes in CRP and albumin were observed in patients who underwent proactive MDD, which is likely due to the initiation of therapy while patients were still in an active phase of disease.

►**Table 2** summarizes the study findings based on proactive and reactive TDM and its variables.

Table 2 TDM of the total sample

Variables	Reactive (n = 26)	Proactive (n = 14)	p-value
			Fisher's Exact
Gender			
Male	6	8	0,042
Female	20	6	
Diagnostic			
Crohn Disease	17	9	1,000
Ulcerative Colitis	9	5	
Calprotectin			
Normal	9	5	1,000
Changed	17	9	
IFX			
Normal	4	2	1,000
Changed	22	12	
AIT			
Positive	3	0	0,521
Negative	11	6	
CRP			
Normal	20	6	0,042
Changed	6	8	
Albumina			
Normal	21	8	0,123
Changed	4	6	

Discussion

As the first anti-TNF agent approved for IBD, IFX has the most experience among gastroenterologists. TDM is currently used in clinical practice to monitor response and guide treatment optimization in the event of drug resistance.[3,8]

Therapeutic drug monitoring (TDM) is an important part of customizing biologic therapy for patients with inflammatory bowel disease (IBD). The purpose of TDM is to inform decisions about whether and when to adjust dosage or consider switching medications for patients who are not responding to therapy. An understanding of the target therapeutic ranges for each agent and how to interpret test results allows healthcare professionals to optimize outcomes for patients receiving biologic therapy. The practice of TDM for managing IBD is currently limited to TNF-Î ± inhibitors; not fully developed for other biologics.

Nine of the sixteen patients with subtherapeutic IFX had high CRP (>5 mg/ml). Subtherapeutic serum IFX in combination with CRP is useful in predicting response loss.[9] Six of the nine patients with elevated CRP had subtherapeutic IFX levels in their serum.

Fecal calprotectin levels were altered in 21 patients, the majority of whom were in the subtherapeutic range. In more than 85% of patients, calprotectin combined with serum IFX predicted relapse.[10] Albumin binding to serum IFX reduces free drug excretion. This study found that albumin levels were normal (74.2%), with a correlation with sub-therapeutic IFX levels (75%), correlating with the literature.[11] The TDM is presented as a valuable decision-making tool for changing behavior based on the amount of serum IFX or ATI present. Serum IFX levels were subtherapeutic in 16 (51.6%) of our patients, with four being proactive, 12 reactive, and only two positive ATI (both reactive). Based on the TDM findings, he advised us to make a change in the treatment after analyzing the serum level or the presence of ITA, demonstrating, and in accordance with the literature, that it is a cost-benefit analysis of the effectiveness of this alternative in the therapeutic approach.[5,12,13]

The loss of anti-TNF response due to immunogenicity, because of the formation of ATI, has a frequency of 6-17%, which is consistent with our series, 6.45%. [14]

In terms of quantitative TDM values, there was a significant difference between the reactive and proactive groups for CRP ($p = 0.027$) and albumin ($p = 0.013$), with proactive MDD patients showing more changes in both CRP and

albumin. Positive ATI, on the other hand, has no effect on clinical remission rate, endoscopic improvement, or CRP level, despite being associated with a higher risk of clinical response loss to IFX and low serum IFX levels [15].

Proactive TDM is a controversial strategy that involves routine monitoring of drug and anti-drug antibody concentrations to achieve therapeutic concentrations and prevent disease outbreaks. As there are currently no proven methods for adjusting the initial loading dose, we are likely underdosing a substantial number of patients initiating biologic therapy. The purpose of proactive TDM is to monitor levels early and provide the opportunity to adjust dosing before they become problematic. Currently, there is insufficient evidence to support this approach, as studies evaluating proactive MDD have failed to attain primary outcomes. Several studies, however, have demonstrated a correlation between higher nadir concentrations of TNF-inhibitors and improved clinical outcomes, including clinical remission and endoscopic remission. In the absence of prospective studies demonstrating that proactive TDM improves clinical outcomes, the approach remains controversial.[9,11,13]

Conclusion

Measuring infliximab serum levels is important in making decisions for monitoring and treating patients who use anti-TNF immunobiological, and this drug should be optimized or suspended based on the findings. TDM is an alternative tool in personalized therapeutic management that offers a cost-benefit analysis. Proactive and reactive TDM, including serum IFX and ATI measurement, is a useful tool that enables more personalized therapy, whereas empiricism allows patients to be exposed to a medication without real benefit. Furthermore, drug spending can be reduced in cases where doses are exceeded.

Conflict of Interest
None.

References

1 Vilela EG, Rocha HC, Moraes AC, et al. Inflammatory Bowel Disease Care in Brasil: How it is Performed, Obstacles Demands from the Physicians Perspective. Arq Gastroenterol 2020;57(04):416–427. [cited 2022–05–06], Epub Dec11, 2020.ISSN 0004–2803

2 Magro F, Gionchetti P, Eliakim R, et al; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohn's Colitis 2017;11(06):649–670. Doi: 10.1093/ecco-jcc/jjx008

3 Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148(07): 1320–9.e3. Doi: 10.1053/j.gastro.2015.02.031

4 Ordás I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther 2012;91(04): 635–646. Doi: 10.1038/clpt.2011.328

5 Papamichael K, Vogelzang EH, Lambert J, Wolbink G, Cheifetz AS. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. Expert Rev Clin Immunol 2019; 15(08):837–848. Doi: 10.1080/1744666X.2019.1630273

6 Roblin X, Boschetti G, Duru G, et al. Distinct Thresholds of Infliximab Trough Level Are Associated with Different Therapeutic Outcomes in Patients with Inflammatory Bowel Disease: A Prospective Observational Study. Inflamm Bowel Dis 2017;23 (11):2048–2053. Doi: 10.1097/MIB.0000000000001223

7 Queiroz NSF, Teixeira FV, Parra RS, Kotze PG. Induction therapeutic drug monitoring regimen with infliximab: a simplified evidence-based algorithm for inflammatory bowel disease. Arq Gastroenterol 2020;57(04):507–510. [Accessed 28 January 2022], Available from: <https://doi.org/10.1590/S0004-2803.202000000-76>. Epub 11 Dec 2020. ISSN 1678–4219

8 Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2015;64(10):1539–1545

9 Moore C, Corbett G, Moss AC. Systematic Review and Meta-Analysis: Serum Infliximab Levels During Maintenance Therapy and Outcomes in Inflammatory Bowel Disease. J Crohn's Colitis 2016;10(05):619–625. Doi: 10.1093/ecco-jcc/jjw007

10 Huang VW, Prosser C, Kroeker KI, et al. Knowledge of Fecal Calprotectin and Infliximab Trough Levels Alters Clinical Decision-making for IBD Outpatients on Maintenance Infliximab Therapy. Inflamm Bowel Dis 2015;21(06):1359–1367

11 Marits P, Landucci L, Sundin U, et al. Trough s-infliximab and antibodies towards infliximab in a cohort of 79 IBD patients with maintenance infliximab treatment. J Crohn's Colitis 2014;8(08): 881–889

12 Paul S, Del Tedesco E, Marotte H, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis 2013;19(12): 2568–2576. Doi: 10.1097/MIB.0b013e3182a77b41

13 Vaughn BP, Martinez-Vazquez M, Patwardhan VR, Moss AC, Sandborn WJ, Cheifetz AS. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. Inflamm Bowel Dis 2014;20(11):1996–2003. Doi: 10.1097/MIB.0000000000000156

14 Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008;134(07):1861–1868. Doi: 10.1053/j.gastro.2008.03.004

15 Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. Am J Gastroenterol 2013;108(01):40–47, quiz 48. Doi: 10.1038/ajg.2012.363

