




# Evaluation of Proactive Therapeutic Drug Monitoring Application in Infliximab Users in Ulcerative Colitis

Gabriela Maria Henz Giovelli<sup>1,2</sup>  Ornella Sari Cassol<sup>1,2</sup> Marcio Lubini<sup>3</sup> Angelina Dantas Costa<sup>1,2</sup>  
Édina Gaviraghi<sup>1,2</sup> Laura de Cezaro Martini<sup>1,2</sup>

<sup>1</sup>Department of Coloproctology and Gastroenterology, Hospital de Clínicas de Passo Fundo (HCPF), Passo Fundo, RS, Brazil.

<sup>2</sup>School of Medicine, ATITUS Educação, Passo Fundo, RS, Brazil.

<sup>3</sup>Department of Gastroenterology, Endoclin Diagnostic Center, Passo Fundo, RS, Brazil.

Address for correspondence Gabriela Maria Henz Giovelli, Medical student, Avenida Sete de Setembro 376, Centro, Zip code: 99010-120, Passo Fundo, RS, Brazil (e-mail: gabigiovelli@gmail.com).

J Coloproctol 2023;43(4):e286–e291.

## Abstract

**Objective** To evaluate the application of proactive pro-drug therapy (TDM) at week six in users of infliximab therapy in ulcerative colitis patients and to analyze the need for further disease optimization.

**Method** This is a retrospective analysis that will be carried out simultaneously at the Hospital de Clínicas de Passo Fundo and at the Endoclin Diagnostic Center in the city of Passo Fundo, with secondary data collection between January 2020 and May 2022. The sample included patients from both sexes, regardless of age, who are being followed up in the services mentioned above, by signing the informed Free and Clarified Consent Term.

**Results** 63.2% of patients required optimization of their treatment based on the serum level assessment at week six.

**Conclusion** Proactive TDM performed at week six benefits patients in order to complete indications for treatment to avoid lack of drug response and complications from the disease.

## Keywords

- ▶ ulcerative colitis
- ▶ colonoscopy
- ▶ infliximab
- ▶ remission induction
- ▶ therapeutic drug monitoring

## Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by recurrent episodes of inflammation of the colonic mucosa, often affecting the rectum and proximal portions of the intestine, usually in a continuous pattern of injury.<sup>1,2</sup> There is a higher prevalence of the disease in developed countries, with an incidence peak between 20 and 40 years old, with a second peak in the elderly population.

During the initial phase of the disease, most patients have bloody diarrhea as the main symptom.<sup>3</sup> Other gastrointestinal symptoms are associated, and in moderate to severe cases, systemic symptoms are present. Clinical manifestations vary according to the spread and severity of the disease.

In patients with moderate to severe UC that are refractory to the use of immunosuppressants, the therapy of choice is immunobiologicals, mainly antitumor necrosis factor (TNF)

received  
August 15, 2023  
accepted  
October 24, 2023

DOI <https://doi.org/10.1055/s-0043-1776889>.  
ISSN 2237-9363.

© 2023. Sociedade Brasileira de Coloproctologia. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

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

alpha (Infliximab). This monoclonal antibody plays an important role in treatment, as it is indicated to reduce signs and symptoms, to induce and maintain clinical remission and mucosal healing, to reduce or discontinue corticosteroid administration and to reduce hospitalizations.<sup>4</sup> However, the pharmacokinetics of these agents and their immunogenicity imply a loss of response over time, due to the reduction of therapeutic levels of the drug, in addition to the appearance of neutralizing antibodies against the drug. Thus, it was analyzed that higher concentrations of these anti-TNF agents, especially during the induction period of treatment, are associated with better long-term therapeutic responses, such as disease remission and mucosal healing.<sup>5</sup>

The proactive therapeutic drug monitoring (TDM) aims to quantify the serum levels of drugs and antibodies immediately before the next infusion of the drug, in this case of infliximab. This assessment aims to provide guidance on the graduation of the administered dose, aiming to prevent the loss of response because of low drug concentrations.<sup>6,7</sup> Thus, it is possible to aim for greater optimization of treatment response and longer time in clinical remission.

Therefore, this study aimed to assess whether patients undergoing proactive TDM in the sixth week of infliximab infusion needed further optimization in their treatment according to their quantified serum level.

## Methods

This is an observational, descriptive study, with a retrospective analysis of a case series and secondary data, of a quantitative nature, obtained through electronic medical records of patients treated at the coloproctology and gastroenterology outpatient clinic, and at the Endoclin Diagnostic Center, both located in southern Brazil, from January 2020 to May 2022, accounting for a total of 19 patients. The sample is non-probabilistic, selected for expedience.

Inclusion criteria are patients of both sexes, over 18 years of age, diagnosed with UC and using infliximab therapy, submitted to proactive TDM in week six of treatment. Patients who were using another immunobiological concomitantly, patients who did not undergo infusion with infliximab at week six, patients who incorrectly used infliximab therapy, patients who did not undergo TDM, patients who underwent proactive TDM at week six, before January 2020 and after May 2022, were not included in this study.

Statistical analysis was performed using the IBM SPSS Statistics software. In the descriptive analysis, to characterize the sample, qualitative variables were presented as absolute frequency (n) and relative frequency (%). For quantitative variables, mean, standard deviation or median and interquartile range (FQI) were identified.

The study followed the norms established by the National Health Council of Brazil and the General Data Protection Law, according to ethical terms. For participation in this research, it was necessary that the patients agreed with the informed consent form provided. Data were collected after approval by the Ethics and Research Committee (CEP) of ATITUS Educação (n° 59664722.2.0000.5319).

## Results

This study included 19 patients diagnosed with UC who were using infliximab and who underwent proactive TDM at week six of treatment. Demographic and clinical characteristics are demonstrated in ►Table 1. Most patients were women, young, self-declared white. However, a significant frequency of middle-aged patients was also noted, especially those over 40 years of age. Most had comorbidities.

It was observed that the presence of a family history of IBD and immune-mediated diseases were not relevant. Among the patients with a positive history for immune-mediated diseases, all had extraintestinal manifestations (EIMs) of the disease, with rheumatological manifestations prevailing, followed by dermatological ones. In this context, it was also noticed that the patients had a relatively long illness and a delay in confirming the diagnosis.

It was observed that faecal calprotectin levels were far above normal levels, more than half of the patients had pancolitis and in the Mayo Score at diagnosis most patients had mucosal ulcerations and spontaneous bleeding, indicating severe disease activity. Regarding medications, it was noticed that all patients were using some type of corticosteroid, since the medication is the first line of treatment in the acute phase of the disease. Furthermore, the excessive use of mesalazine and azathioprine are justified because, in addition to being part of the first line of treatment, they are also used in the maintenance phase.

In assessing the serum level of infliximab, it was seen that few patients were able to reach a level considered adequate for treatment. Finally, data on the Mayo Clinical score were computed at week six of treatment, most had moderate disease activity with only one patient experiencing remission. It was possible to observe the relationship between low serum levels of Infliximab, high Mayo clinical score and the need for dose optimization in order to maintain the clinical response to treatment.

## Discussion

The IBD represented by Crohn's disease and UC are a chronic clinical entity of the gastrointestinal tract, and present clinical manifestations that vary according to the extension and severity of the disease. Therefore, patients with moderate and severe involvement due to UC benefit from the use of monoclonal antibodies, such as infliximab, which promotes, among many other benefits, the healing of the colon and rectum mucosa. In this context, TDM helps to prevent loss of response to treatment, as well as clinical remission.

The characteristics of the population in this study were like those described in other literature. The average age found in the study of 43.74 years is in accordance with the description of a higher incidence of UC in people over 40 years of age.<sup>8</sup> The female gender and the white race were predominant, as found in other studies, especially those carried out in the southern region of Brazil, where the presence of the female population and European immigration also predominate.<sup>9,10</sup>

**Table 1** Characteristics of the study population

N	19
Female (%)	11 (57.9)
Age, years (FQI)	43,74 (22-69)
Caucasians (%)	17 (89.5)
IBD family history (%)	2 (10.5)
Family history of immune-mediated disease (%)	2 (10.5)
Personal history of immune-mediated disease (%)	6 (31.6)
Comorbidities (%)	10 (52.6)
Systemic arterial hypertension (%)	7 (36.8)
Obesity (%)	3 (15.8)
Depression (%)	4 (21.1)
Dyslipidemia (%)	1 (5.3)
Diabetes mellitus (%)	1 (5.3)
Disease duration (months) (FQI)	68 (2-204)
Time from symptoms to diagnosis (months) (FQI)	7 (1-60)
Pancolitis (%)	12 (63.2)
Faecal calprotectin (FQI)	1,759 mcg/g (292-6,000)
Mayo endoscopic score 3 (%)	16 (84.2)
Corticosteroids (%)	19 (100)
Mesalazine (%)	17 (89)
Azathioprine (%)	14 (73.7)
Vedolizumab (%)	3 (15.8)
Methotrexate (%)	1 (5.3)
Serum level at week six (FQI)	7.8 µg/mL (1.0-20.0)
Treatment optimization (%)	12 (63.2)
Mayo 8 score (%)	8 (42.1)
Mayo 7 score (%)	6 (31.6)
Mayo 6 score (%)	2 (10.5)
Mayo 3 score (%)	2 (10.5)
Mayo 2 score (%)	1 (5.3)

Abbreviations: FQI, interquartile range; IBD, inflammatory bowel disease.

Regarding the family history of IBD, a low number was found. This low incidence may be associated with a current increase in IBD cases and new environmental factors that may be related to the onset of the disease.<sup>11,12</sup>

The results regarding the personal history of immune-mediated disease highlighted the presence of EIMs of UC, with a predominance of peripheral spondyloarthritis and pyoderma gangrenosum.<sup>13,14</sup> This differs from what is described in other studies, where arthralgia is the most common EIM, although in this sample the occurrence of psoriasis and erythema nodosum as EIMs were also observed, thus prevailing dermatological manifestations. This fact may have been influenced by the location of the diagnosis, since this is recognized as a reference for the evaluation of dermatological diseases and, therefore, with a greater number of such diagnoses.

About the duration of the disease and the period between the onset of symptoms and the diagnosis, the previous

literature describes a higher average than that found in this study. This finding may be due to the delay in accessing specialized health services, as well as to regional differences in each study. Despite this, it was not possible to corroborate these data due to the lack of literature on the subject.<sup>10</sup>

Regarding comorbidities, it is not clear whether obesity can be a risk factor for developing IBD.<sup>15</sup> Another prevalent comorbidity was depression, which may be related to the fact that UC is a chronic disease, with an often-unpredictable course, affecting patients' quality of life, especially their mental health. Thus, these patients have a high level of stress and have an increased risk of depression when compared to the general population.<sup>16</sup> Regarding comorbidities such as systemic arterial hypertension, diabetes mellitus and dyslipidemia, no literature was found to correlate these comorbidities with the disease.

The extent of the disease has a direct influence on the management and choice of therapies for the patient. It

should be noted the high prevalence of extensive colitis, both in this research and in other studies, even in the use of immunobiologicals. This finding demonstrates a presentation of the disease with a severe clinical condition that is refractory to the use of other medications.<sup>9,17</sup>

Faecal calprotectin is a highly sensitive marker of endoscopically active intestinal inflammation. Its concentration is higher in patients with active disease when compared to those with inactive disease. In this research, the median found was 1,759 mcg/g, attesting to the high sensitivity of the test and the high degree of mucosal inflammation. However, calprotectin reflects neutrophil excretion into the lumen. Thus, other diseases of the digestive tract can alter this test, making colonoscopy essential, especially for the diagnosis.<sup>18,19</sup>

The endoscopic alterations observed in more than 84% of the patients, through the Mayo endoscopic score performed at diagnosis, considered cases with the presence of ulcerations and spontaneous bleeding to be severe.<sup>1,20</sup> These data were useful in predicting the need for intensified drug treatment or the need for surgical intervention. In addition to facilitating the visualization of mucosal healing, indicating absence of disease or inactivity. So, it is possible to perceive a better response to clinical treatment and a decrease in the risk of hospitalization and surgical intervention.

Regarding the use of medication, compared to other studies, the data were very similar, recommending the use of corticosteroids, since these provide more immediate relief of symptoms.<sup>21</sup> Mesalazine and azathioprine have also been widely used as they aid in initial therapy and clinical remission.<sup>16,22,23</sup>

Some patients present in the research used vedolizumab, however, its use was discontinued due to loss of drug response. This fact may be due to several factors, such as the development of anti-drug antibodies, intrinsic mediation factors and alternative inflammatory pathways. Methotrexate is less recommended because it has not been shown to be superior to placebo in inducing or maintaining remission of active chronic disease.<sup>23-25</sup>

The serum level of infliximab can be influenced by several factors, such as disease severity, patient characteristics, drug pharmacodynamics and pharmacokinetics, and drug interactions.<sup>26</sup> In the TAXIT study, patients were dose-optimized to remain at a threshold of 3-7 µg/mL. Those patients who had low concentrations of the drug and performed treatment optimization achieved a higher proportion of clinical disease remission. This demonstrates that the use of proactive TDM for treatment optimization can be beneficial.

Another fact found in TAXIT was that patients who did not undergo proactive TDM, after one year had higher rates of anti-drug antibodies, as well as minimal or undetectable levels of infliximab, indicating a greater risk of disease reactivation and treatment failure. Whereas drug concentrations, particularly in the induction phase, help to achieve treatment goals, especially clinical remission and mucosal healing.<sup>27</sup>

In that same study, optimization was observed to increase the number of patients in clinical remission from 65% pre-optimization to 88% post-optimization.<sup>28</sup> However, the eval-

uation of clinical remission after week six of treatment was not analyzed in this research and, therefore, it was not possible to compare it with the studies mentioned above.

In this study, it was noted that of the 19 patients evaluated, 12 (63.2%) required optimization, with the value of 10 µg/mL used as a basis to indicate the need for optimization. This value was defined because a single serum level measurement taken at week six is able to stratify patients who benefit or not from treatment optimization.<sup>27</sup> Thus, the value of 10 µg/mL was defined as an adequate threshold to consider maintaining the same dose of drug in the next infusions.

Other literature data state that significant serum levels at week six are associated with higher short-term mucosal healing rates. Therefore, patients with serum levels below 10 µg/mL would benefit from therapeutic strategies to avoid future loss of response to treatment and the development of anti-drug antibodies.<sup>29</sup>

The evaluation of the Mayo clinical score, performed at week six, showed that 84.2% of the patients had moderate disease activity ranging from score 6 to 8. Of the others (15.8%), two had mild disease and only one had remission at week six of treatment. However, some factors such as the presence of pancolitis, an endoscopic Mayo score of 3 and acute severe colitis showed lower levels of infliximab, and therefore, a higher clinical score. It was also identified that only the serum level presented at week six was an independent factor associated with short-term mucosal healing.<sup>29</sup>

There was a significant number of patients who required optimization in their treatment, but it was expected that the Mayo clinical score would show slightly higher values, as it assesses disease activity considering both endoscopic findings and clinical signs. Also, it was observed that no patient had a severe condition and that there was a clinical improvement of symptoms and signs of the disease. However, it was not possible to corroborate these data, due to the lack of studies that specifically investigated the Mayo clinical score at week six of treatment.

Therefore, a single infliximab serum level measurement at week six, at the end of induction, may benefit many patients throughout the maintenance phase of treatment, if dose optimization is performed early. This strategy could minimize the chance of disease reactivation, hospitalizations due to severe conditions, and loss of response to the drug.<sup>27</sup>

## Conclusion

This study demonstrated the predominance of UC in females, Caucasians, with a mean age of 43,74 years. Patients had predominantly pancolitis, an endoscopic Mayo score of 3, high faecal calprotectin levels at diagnosis, and extensive use of corticosteroids, attesting to severe disease activity. It was observed that there is a very low correlation between family history of IBD and immune-mediated disease with the presence of UC, indicating that environmental factors may be more related to the appearance of the disease. Furthermore, there is no clear association between the

comorbidities presented by the patients and the presence of UC.

The benefit of proactive TDM in UC can be evaluated by analyzing the serum level of infliximab at week six. The benefit that proactive TDM performed at the end of the induction phase can bring to the patient has been demonstrated, allowing earlier and more individualized management. Thus, it was observed that optimizing treatment earlier led to a better clinical response, allowing these patients to achieve full endoscopic and histological remission after optimization.

#### Conflicts of Interest:

None.

#### References

- Saad-Hossne R, Coy CSR. Atualização em doenças inflamatórias intestinais: conectando ciência à prática diária: curso de atualização do GEDIIB na SBAD 2019. São Paulo: Office; 2019
- Pepercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. Up To Date 2022. [accessed on May 29 2023]. Available from: [https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-ulcerative-colitis-in-adults?search=retocoliteulcerativa&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-ulcerative-colitis-in-adults?search=retocoliteulcerativa&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1)
- Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas da Retocolite Ulcerativa. Brasília: Ministério da Saúde; 2019. [accessed on June 01 2023]. Available from: [https://bvsms.saude.gov.br/bvs/publicacoes/protocolo\\_clinico\\_terapeuticas\\_retocolite\\_ulcerativa.pdf](https://bvsms.saude.gov.br/bvs/publicacoes/protocolo_clinico_terapeuticas_retocolite_ulcerativa.pdf)
- Nemoz B, Ternant D, Bailly S, et al. New steps in infliximab therapeutic drug monitoring in patients with inflammatory bowel diseases. *Br J Clin Pharmacol* 2019;85(04):722–728. Doi: 10.1111/bcp.13845
- Dreesen E, Faelens R, Van Assche G, et al. Optimising infliximab induction dosing for patients with ulcerative colitis. *Br J Clin Pharmacol* 2019;85(04):782–795. Doi: 10.1111/bcp.13859
- Scharnhorst V, Schmitz EMH, van de Kerkhof D, Derijks LJJ, Broeren MAC. A value proposition for trough level-based anti-TNF $\alpha$  drug dosing. *Clin Chim Acta* 2019;489:89–95. Doi: 10.1016/j.cca.2018.11.038
- Syversen SW, Jørgensen KK, Goll GL, et al. Effect of therapeutic drug monitoring vs standard therapy during maintenance infliximab therapy on disease control in patients with immune-mediated inflammatory diseases: a randomized clinical trial. *JAMA* 2021;326(23):2375–2384. Doi: 10.1001/jama.2021.21316
- Cassol OS, Zobot GP, Saad-Hossne R, Padoin A. Epidemiology of inflammatory bowel diseases in the state of Rio Grande do Sul, Brazil. *World J Gastroenterol* 2022;28(30):4174–4181. Doi: 10.3748/wjg.v28.i30.4174
- Click B, Barnes EL, Cohen BL, et al. Objective disease activity assessment and therapeutic drug monitoring prior to biologic therapy changes in routine inflammatory bowel disease clinical practice: TARGET-IBD. *BMC Gastroenterol* 2022;22(01):71. Doi: 10.1186/s12876-022-02143-x
- da Silva BC, Lyra AC, Mendes CMC, et al. The Demographic and Clinical Characteristics of Ulcerative Colitis in a Northeast Brazilian Population. *BioMed Res Int* 2015;2015:359130. Doi: 10.1155/2015/359130
- Farmer RG, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. *Dig Dis Sci* 1993;38(06):1137–1146. Doi: 10.1007/BF01295733
- Portela F, Magro F, Lago P, et al. Ulcerative colitis in a Southern European country: a national perspective. *Inflamm Bowel Dis* 2010;16(05):822–829. Doi: 10.1002/ibd.21119
- Lakatos L, Pandur T, David G, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. *World J Gastroenterol* 2003;9(10):2300–2307. Doi: 10.3748/wjg.v9.i10.2300
- Brynskov J, Binder V. Arthritis and the gut. *Eur J Gastroenterol Hepatol* 1999;11(09):997–999. Doi: 10.1097/00042737-199909000-00008
- Chan SSM, Luben R, Olsen A, et al. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). *Am J Gastroenterol* 2013;108(04):575–582. Doi: 10.1038/ajg.2012.453
- Hashash JG, Vachon A, Ramos Rivers C, et al. Predictors of Suicidal Ideation Among IBD Outpatients. *J Clin Gastroenterol* 2019;53(01):e41–e45. Doi: 10.1097/MCG.0000000000001094
- 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
- Mosli MH, Zou G, Garg SK, et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2015;110(06):802–819, quiz 820. Doi: 10.1038/ajg.2015.120
- Xiang JY, Ouyang Q, Li GD, Xiao NP. Clinical value of fecal calprotectin in determining disease activity of ulcerative colitis. *World J Gastroenterol* 2008;14(01):53–57. Doi: 10.3748/wjg.14.53
- Shergill AK, Lightdale JR, Bruining DH, et al; American Society for Gastrointestinal Endoscopy Standards of Practice Committee. The role of endoscopy in inflammatory bowel disease. *Gastrointest Endosc* 2015;81(05):1101–21.e1, 13. Doi: 10.1016/j.gie.2014.10.030
- Cohen RD, Stein AC. Management of moderate to severe ulcerative colitis in adults. Up To Date 2021. [accessed on May 15 2023]. Available from: [https://www.uptodate.com/contents/management-of-moderate-to-severe-ulcerative-colitis-in-adults?search=retocoliteulcerativa&source=search\\_result&selectedTitle=4~150&usage\\_type=default&display\\_rank=4](https://www.uptodate.com/contents/management-of-moderate-to-severe-ulcerative-colitis-in-adults?search=retocoliteulcerativa&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4)
- A-Rahim YI, Farrell R. Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults. Up To Date 2020. [accessed on May 18 2023]. Available from: [https://www.uptodate.com/contents/overview-of-dosing-and-monitoring-of-biologic-agents-and-small-molecules-for-treating-ulcerative-colitis-in-adults?search=retocoliteulcerativa&source=search\\_result&selectedTitle=7~150&usage\\_type=default&display\\_rank=7](https://www.uptodate.com/contents/overview-of-dosing-and-monitoring-of-biologic-agents-and-small-molecules-for-treating-ulcerative-colitis-in-adults?search=retocoliteulcerativa&source=search_result&selectedTitle=7~150&usage_type=default&display_rank=7)
- Fucilini LMP, Genaro LM, Sousa DCE, Coy CSR, Leal RF, Ayrizono MLS. Epidemiological profile and clinical characteristics of inflammatory bowel diseases in a Brazilian referral center. *Arq Gastroenterol* 2021;58(04):483–490. Doi: 10.1590/S0004-2803.202100000-87
- Chande N, Wang Y, MacDonald JK, McDonald JWD. Methotrexate for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2014;2014(08):CD006618. Doi: 10.1002/14651858.CD006618.pub3
- Oren R, Arber N, Odes S, et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter

- trial. *Gastroenterology* 1996;110(05):1416–1421. Doi: 10.1053/gast.1996.v110.pm8613046
- 26 Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic Drug Monitoring to Guide Infliximab Dose Adjustment is Associated with Better Endoscopic Outcomes than Clinical Decision Making Alone in Active Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2017;23(07):1202–1209. Doi: 10.1097/MIB.0000000000001126
- 27 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. Doi: 10.1590/S0004-2803.202000000-76
- 28 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
- 29 Papamichael K, Van Stappen T, Vande Casteele N, et al. Infliximab Concentration Thresholds During Induction Therapy Are Associated With Short-term Mucosal Healing in Patients With Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2016;14(04):543–549. Doi: 10.1016/j.cgh.2015.11.014