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# The evaluation of infliximab trough level favors maintenance therapy of patients with inflammatory bowel disease

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**ABSTRACT – Background –** Crohn's disease (CD) and ulcerative colitis (UC) are chronic diseases that result from the deregulation of the mucosal immune system of the gastrointestinal tract. The use of biological therapies, including infliximab (IFX), is one of the strategies to treat both CD and UC. The IFX treatment is monitored by complementary tests, namely: fecal calprotectin (FC); C-reactive protein (CRP); and endoscopic and cross-sectional imaging. Besides, serum IFX evaluation and antibody detection are also used. **Objective –** To evaluate trough levels (TL) and antibodies in a population with inflammatory bowel (IBD) disease undergoing treatment with IFX, and the factors that might impact the treatment effectiveness. **Methods –** Retrospective, cross-sectional study with patients with IBD that were assessed for TL and antibody (ATI) levels in a southern Brazilian hospital, from June 2014 to July 2016. **Results –** The study assessed 55 patients (52.7% female) submitted to serum IFX and antibody evaluations (95 blood samples, 55 first test; 30 second test, and 10 as third testing. Forty-five (47.3%) cases were diagnosed with CD (81.8%), and ten with UC (18.2%). Serum levels were adequate in 30 samples (31.57%), subtherapeutic in 41 (43.15%), and supratherapeutic in 24 (25.26%). IFX dosages were optimized for 40 patients (42.10%), maintained for 31 (32.63%), and discontinued for 7 (7.60%). The intervals between infusions were shortened in 17.85% of the cases. In 55 tests (55.79%), the therapeutic approach was exclusively defined according to IFX and/or serum antibody levels. The assessment of patients one year later indicated that: the approach was maintained with IFX for thirty-eight patients (69.09%); the class of biological agent was changed for eight (14.54%); changes using the same class of biological agent occurred for two patients (3.63%); the medication was discontinued and not replaced for three patients (5.45%), and four patients (7.27%) were lost to follow-up. **Conclusion –** There were no differences in TL between groups with or without immunosuppressants, serum albumin (ALB), erythrocyte sedimentation rate (ESR), FC, CRP, and endoscopic and imaging examinations. Current therapeutic approach could be maintained for almost 70% of patients. Thus, serum and antibody levels are a useful tool in the follow-up of patients undergoing maintenance therapy and after treatment induction in patients with inflammatory bowel disease.

**Keywords –** Crohn's disease; ulcerative colitis; infliximab; anti-infliximab antibody; monitoring; biological therapy.

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## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) that occur in genetically predisposed patients. They result from the deregulation of the mucosal immune system of the gastrointestinal tract and are associated with triggering environmental factors[1-2]. Symptoms can vary, e.g. diarrhea, abdominal pain, weight loss, mucus and/or blood in feces, and, in the case of CD, perineal manifestations[2-4]. Treatment include using immunosuppressants, as well as biological therapies, such as infliximab (IFX), vedolizumab and ustekinumab[1], or even surgical procedures[2-4].

Patients with IBD have elevated tumor necrosis factor (TNF), a proinflammatory cytokine[5]. Therefore, anti-TNF, such as IFX, a chimeric murine-human IgG1 (75% human and 25% murine), is indicated in more severe forms of the diseases[6]. The murine component is responsible for the immunogenicity of the drug and the formation of anti-IFX antibodies (ATI), which may reduce the effectiveness of the IFX therapy[3,4,7,8]. Periodic assessment of the response to IFX therapy should be performed through IFX trough levels, ATI detection, and assessment of the degree of bowel inflammation.

The aim of this study was to assess the response of patients with IBD to IFX therapy and its adequacy in a southern Brazilian center. The objectives are to evaluate the advantages of single and/or sequential evaluation of TL of IFX and ATI in IBD patients undergoing IFX treatment, as well as to correlate serum TL and ATI presence with concomitant immunosuppressive medications, and laboratory, endoscopic and imaging studies. Another goal is to evaluate medical follow-up one year after the IFX evaluation.

## METHODS

This is a retrospective cross-sectional study conducted through the review of medical records of patients with CD or UC treated at the IBD ambulatory of *Hospital Nossa Senhora das Graças*, located in Curitiba, state of Paraná, Brazil. The patients were submitted to the assessment of IFX and ATI serum levels from June 2014 to July 2016. The research was approved by the Human Research Ethics Committee of the Hospital of Clinicas, at the Federal University of Paraná.

All patients were diagnosed with CD or UC according to clinical assessments, endoscopic, imaging examinations and histology[2,5,9]. The blood samples for IFX TL were collected before the IFX infusion, in some cases, after the induction phase. They were processed by the UZ Leuven, a university hospital in Belgium, using the Infliximab ELISA method (Laboratory for Pharmaceutical Biology, KU Leuven, distributed by apDia)[8,10-13].

The TL were considered therapeutic when they ranged between 3 and 7 µg/mL, supratherapeutic when they were above 7 µg/mL, and subtherapeutic if they were lower than 3 µg/mL, with the lowest limit of detection being 0.3 µg/mL. The ATI levels were considered as follows: a) absent; b) low level (<8 µg/mL); or c) high level (> or equal to 8 µg/mL)[12,14,15].

Some patients underwent more than one IFX TL evaluation (maximum three), mainly for greater control of therapeutic response, suspected therapeutic failure or after dose optimization.

The description and analysis of the immediate conduct was conducted right after each collection, as well as its correlation with TL and ATI. In addition to the relationship between TL and ATI levels with: concomitant use of immunosuppressant, CRP, ESR, FC, ALB, body mass index (BMI), previous and current smoking, disease-related surgery, endoscopic and imaging examinations. The number of times above the reference value (RV) was established for analysis of the CRP result.

Finally, the medical conduct adopted was described one year after the last IFX evaluation and its correlation with the TL.

We used the chi-square and Fisher test to assess the association between variables, and *P*-values <0.05 indicated statistical significance. Data were analyzed using the IBM SPSS Statistics software, Version 20.0, Armonk, NY: IBM Corp and Software Statistic R (R Core Team, 2020, Version 3.6.3)

## RESULTS

We obtained 95 blood samples from 55 patients. Regarding the samplings, 30 were repeated once

and 10 were repeated twice, with a mean of 1.72 samples per patient.

As to the profile of the patients assessed, 29 were female (52.72%) and 26 were male (47.27%), with a mean age of 41.2 years, and median of 40 years. Forty-five cases were diagnosed with CD (81.8%) and 10 with UC (18.2%). FIGURE 1 illustrates the data of the patients with CD according to the Montreal classification.

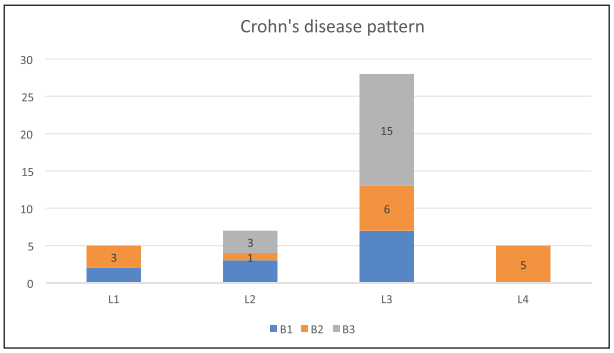


**FIGURE 1.** Correlation between disease location and pattern (L1 – terminal ileum; L2 – colon; L3 – ileocolonic; L4 – upper GIT) and pattern (B1 – non-stenosing or non-penetrating; B2 – stenosing; B3 – penetrating) of the patients with Crohn's disease.

The duration of IFX treatment ranged from two months to nine years, with a mean of 4.09 years.

Regarding the TL determined in all 95 samples, it was observed that the mean value of IFX was 4.43 mg/dL, and the value of ATI was 7.67 mg/dL.

The drug dosage was therapeutic in 30 samples (31.57%), subtherapeutic in 41 (43.15%), and supra-therapeutic in the remaining 24 (25.26%) samples. The clinical approach was done as follows: IFX optimized in 40 (42.10%) cases; maintained in 31 (32.63%); discontinued in 7 (7.60%); and interval increase between infusions in 17 (17.85%). Due to the detection of ATI, four patients had to discontinue the use of IFX (TABLE 1).

For 13 patients, the sampling was performed shortly after the end of the induction phase (week 14 in weeks 0.2 and 6); no ATI was observed in this group of patients. In 5 (38.46%), the TL was at the therapeutic level.

The assessment (of the patients) 1 year after the last sampling indicated that, in 38 (69.09%) cases, the IFX dose could be maintained; 8 (14.54%) required switching to another biological class; 2 (3.63%) required switching to another anti-TNF; for 3 (5.45%) patients the medication was discontinued and not replaced due to clinical stability; and 4 (7.27%) cases lost follow-up.

**TABLE 1.** Therapeutic approaches adopted.

| Serum level | Nº (%) | Process |
|---|---|---|
| Therapeutic Nº 30 (31.57%) | 24 (80) | Maintained |
| | 4 (13.33) | Optimized*1 |
| | 1 (3.33) | Discontinued*1 |
| | 1 (3.33) | Increased interval*2 |
| Subtherapeutic Nº 41 (43.15%) | 33 (80.48) | Optimized |
| | 5 (12.19) | Discontinued (4*3; 1*1) |
| | 3 (7.31) | Maintained*2 |
| | 16 (66.66) | Increased interval*2 |
| | 3 (12.5) | Decreased interval *4 |
| | 1 (4.16) | Discontinued*1 |
| | 4 (16.66) | Maintained*5 |

*1: patients with persistent inflammatory bowel disease symptoms; *2: patients with good clinical stability; *3: high levels of anti-infliximab antibody; *4: therapeutic failure; *5: medical decision.

ATIs were found in 12 (12.63%) among the 95 samplings performed, with four exhibiting high levels and eight samples presenting low levels. Of these patients, four had their medication discontinued due to high levels of ATI. IFX was optimized in five cases. The drug was maintained for one patient by clinical decision, and, in another case, (the IFX treatment) was discontinued due to disease activity.

In general, the approaches were determined in 53 (55.79%) samplings according to the IFX and/or ATI levels.

Fifty-five patients were included in the first sampling, and their distribution can be observed in FIGURE 2. Therapeutic levels were found in 16 patients, subtherapeutic in 28, and supra-therapeutic level in 11 patients. The clinical management was maintained for 15 patients and optimized for 28. The ATIs were present in 10 patients, four of which exhibited high levels and had, therefore, IFX discontinued.

A second sampling was collected in thirty patients; TL were adequate for 12, subtherapeutic for nine, and supratherapeutic for nine patients. The presence of ATI was observed in one patient only.

A third sampling was performed in 10 cases. The TL were adequate for two patients, subtherapeutic for four patients, and supratherapeutic for the other four. The ATI were found in one case.

The complementary exams performed in the total population were (FIGURE 3):

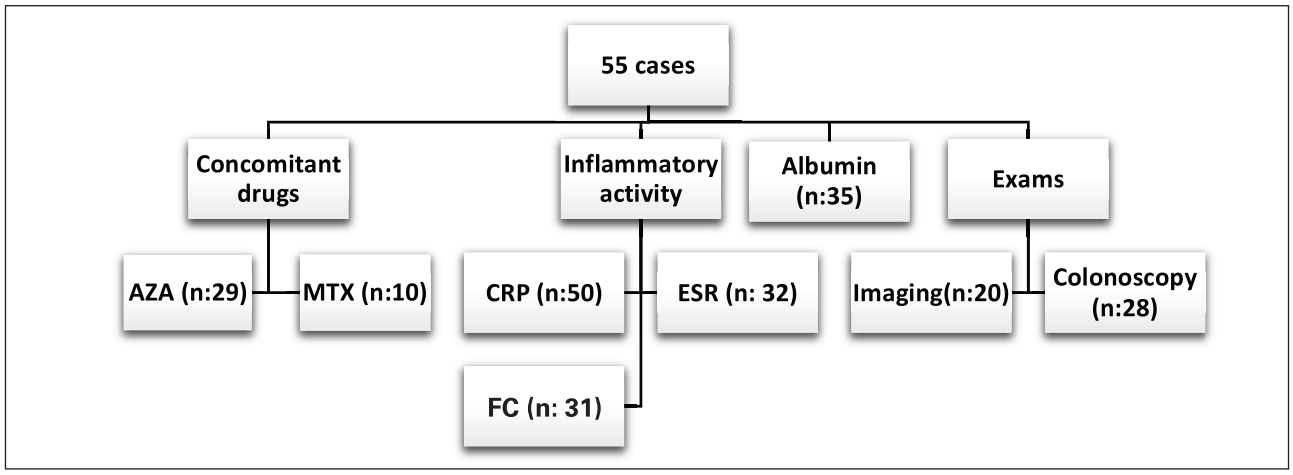


**FIGURE 2.** Flowchart of distribution of patients in the study based on the first sampling.
AZA: azathioprine; MTX: methotrexate; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, FC: fecal calprotectin.

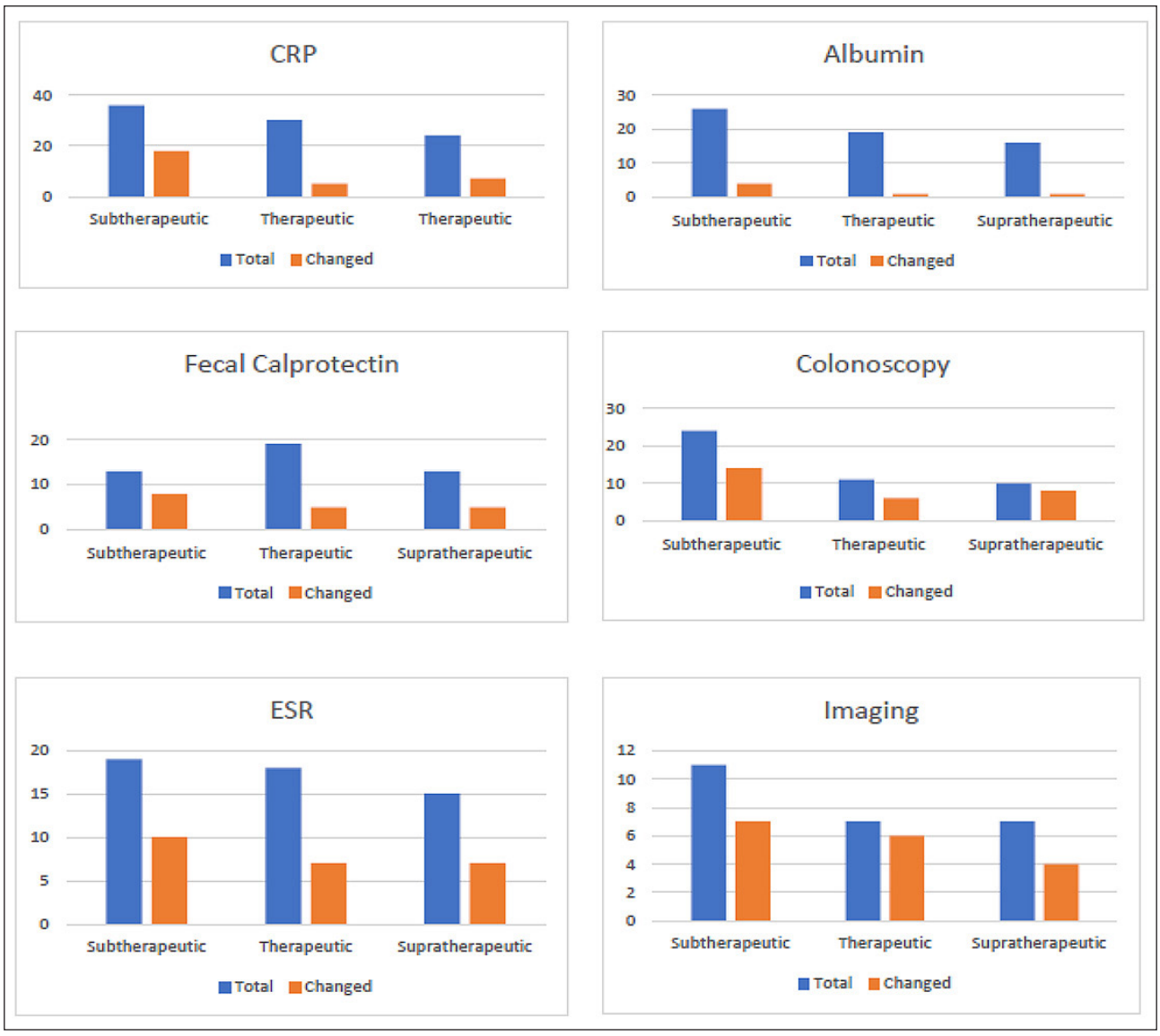


**FIGURE 3.** Changes indicated by the complementary examinations according to IFX levels.
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

The population that underwent the first sampling (55 patients) was assessed for the statistical analysis (FIGURE 2). The correlation between the TL and immediate approach indicated that the *P*-value was <0.001 (FIGURE 4). Therefore, there was evidence that the immediate approach was depended on the IFX levels, with the approach maintained in about 80% of patients with therapeutic IFX levels.

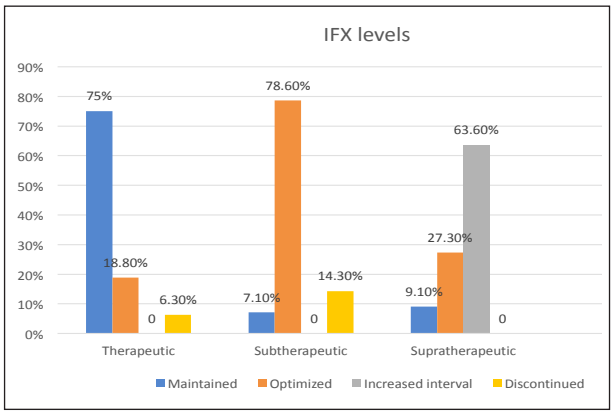


**FIGURE 4.** Immediate therapeutic approach according to IFX levels.

The correlation between TL and the use of azathioprine (AZA), CRP, FC, ESR, immunosuppressants, ALB, BMI, previous and current smoking, disease-related surgery and imaging exams did not indicate significant values, or the sample size was small for the calculation (TABLE 2). We compared the group of 22 patients for whom the immediate approach was optimized with the group that had the approach modified exclusively due to the IFX levels – i.e. discontinued due to ATI – and supratherapeutic with increased intervals, totaling 33 patients. This analysis indicated that the immediate approach optimized for the subtherapeutic level was significant for this population (66.7%; *P*<0.001; interval [50.6 and 82.8%] and 95% confidence level (TABLE 3).

**TABLE 3.** Therapeutic approach changed due to IFX levels.

| Classification | n | % |
|---|---|---|
| Subtherapeutic serum level with optimized immediate approach | 22 | 66.7% |
| Subtherapeutic serum level with discontinued immediate approach | 4 | 12.1% |
| Supratherapeutic serum level with immediate approach and increased interval | 7 | 21.2% |
| Total | 33 | 100% |

In the absence of ATI, the therapeutic approach was maintained in 76.7% of the cases, with *P*=0.005 (TABLE 2).

Regarding the therapeutic approach one year later, the correlation of the patients with subtherapeutic level (n=28) indicated that the process was maintained in fifteen cases (53.6%) with statistical significance (*P*<0.001), 95% confidence level (35.1%; 72.0%) and 95% significance (TABLE 2).

**TABLE 2.** Overview and statistical analysis.

| | Assessment | | Statistics | | | | |
|---|---|---|---|---|---|---|---|
| | 1st sampling (n = 55) | 2nd sampling (n = 30) | 3rd sampling (n = 10) | IFX (*P*) | ATI (*P*) | Therapeutic level | Subtherapeutic level |
| CRP (RV) | 17 (50) | 9 (30) | 4 (10) | 0.423 | 0.782 | 0.357 | |
| ALB (g/dL) | 4.06 (35) | 4.15 (19) | 4.18 (7) | 0.373 | N/A | 0.555 | |
| ESR (mm/h) | 23.26 (32) | 19.76 (17) | 2 (3) | 0.662 | 0.766 | 0.71 | |
| FC (ug/g) | 359.16 (31) | 64.73 (19) | 262.88 (7) | 0.661 | 0.9 | 0.457 | |
| COL | 21 (29) | 5 (13) | 2 (3) | N/A | N/A | N/A | |
| RAD | 15 (20) | 5 (2) | | 0.329 | N/A | 0.136 | |
| AZA | 29 | 19 | 6 | 0.628 | 0.085 | 0.352 | |
| MTX | 10 | 4 | 2 | 0.761 | N/A | 0.484 | |
| IFX (mg/dL) | 4.43 | | | | | | |
| ATI (mg/dL) | 7.67 | | | | | | |
| time (years) | 4.09 | | | | | | |
| ATI % | 18.18 | 3.33 | 10 | | | | |
| Immediate approach | | | | <0.001 | N/A | <0.001 | <0.001 |
| Final approach | | | | 0.082 | 0.005 | | <0.001 |

ATI: anti-infliximab antibodies; ALB: albumin; AZA: azathioprine; FC: fecal calprotectin; COL: colonoscopy; IFX: Infliximab; MTX: methotrexate; n: number of patients; CRP: C-reactive protein; RAD: radiological examinations; ESR: erythrocyte sedimentation rate; RV: reference value; N/A: not available.

## DISCUSSION

IFX was the first anti-TNF biologic agent used in the treatment of IBD. It is a chimeric recombinant monoclonal IgG1 that binds with high affinity to human TNF[16].

Despite the good outcomes at the beginning of treatment, it was noticed that, over time, some patients stop responding to the therapy[11,17]. There are alternatives to correct this loss of response, such as treatment optimization, immunosuppressant addition, or changing the biological agents. Optimization can be achieved empirically or by monitoring TL and detecting ATI[18-22].

One cause of loss of response is the formation of ATIs, which, according to Baert et al. and Van Stappen et al., are anti-IFX antibodies that occur at a frequency of 6 to 17%[23-25]. The ATIs bind to IFX and form immune complexes[26-28].

ATIs usually develop in the first 12 months of anti-TNF treatment. In this study, patients with positive ATI had been using IFX for 3.8 years on average, ranging from 1 to 7 years[17]. There are ways to prevent the formation of ATIs, such as infusion at appropriate intervals and doses, and use of immunosuppressants AZA and methotrexate (MTX)[21,29-32]. In this study, ATIs were present in 12.63% of the cases. Comparing the samplings, we noticed a decrease in the frequency of ATI with proactive therapy.

In our study, only 31.57% of the samples had adequate IFX levels. The main reason for discontinuation of medication was the presence of ATIs. We observed 12.63% of ATIs[4,20,32]. In the TAXIT, the mean level of ATI was 5.2 mg/dL[33], whereas in our study, it was 7.67 mg/dL.

The study showed that, among the ninety-five samplings performed, 53 (55.79%), in general, and 33 (60%), in the first sampling, had their therapeutic approaches modified based solely on IFX and ATI levels, i.e. a proactive strategy was adopted[24,34-36].

The TAXIT study suggests that IFX dosage should be reassessed every 6 months, and other studies suggest at least one assessment during the first year of the maintenance phase. In our study, the TL was evaluated in, at least, one sampling, and, in cases in which it was necessary, the levels were evaluated up to two more times. The evaluation could be performed for some patients after the induction phase. In this group, even after shortened intervals for the drug administration, there were patients with subtherapeutic levels. According to Heron et al., it is likely that for each patient there will be an appropriate serum level of medication to induce response, resulting in a personalized therapy[27].

In this study, the proactive strategy helped to maintain IFX therapy, given that, among the 55 patients assessed, 38 (69.09%) were able to maintain their medication and/or could discontinue it due to clinical stability. Therefore, proactive therapy was beneficial in 41 patients (74.54%). Also, among the twenty-eight patients with subtherapeutic levels (<3 mg/dL) of IFX in the first sampling, twenty-two needed to have their therapeutic approach optimized. About one year later, the therapeutic approach could be maintained in 13 of those patients, and the drug could be discontinued in one patient due to clinical and endoscopic stability. Thus, in 59.09% of these cases the therapeutic approach could be maintained using IFX.

On the other hand, a recent prospective study conducted by D'Haens et al. indicated that patients with CD did not exhibit differences in corticosteroid-free rate and disease remission, comparing symptom-based optimization with that based on TL[37].

The IFX level in conjunction with serum CRP concentration can predict loss of response to IFX. A systematic review conducted by Moore et al. showed that the mean CRP was higher for patients with subtherapeutic IFX levels[38,39]. The same result was found by Cornillie et al. in which patients with adequate levels of IFX had appropriate CRP levels and patients with subtherapeutic levels had high CRP levels.

Kotze et al. found FC values of 50.5 µg/g in IBD, 405 µg/g in CD, and 457 µg/g in UC, with no statistical difference between CD and UC, but with a difference between those patients with active disease or remission[40,41]. Nevertheless, Vieira et al. found levels of 686 µg/g in patients with IBD[42]. In this study, we found an average FC of 236.73 µg/g, with 438 µg/g in UC and 355.36 µg/g in CD. According to some studies, FC combined with IFX level is able to predict disease relapse in over 85% of patients[19,43].

In the assessed population, we did not observe a relationship between the levels of IFX and ATI and the use of immunosuppressive drugs. It is worth mentioning that Parra et al. found the same result[36].

A limiting factor for this study was the fact that it was retrospective and performed with a small number of patients. Certainly, further prospective studies assessing larger samples are necessary, especially to assess the variables that may interfere with these dosages.

## CONCLUSION

Finally, this study showed that the evaluation of IFX and ATI levels was a useful tool to provide greater safety and objectivity to IFX dose adjustment in patients with IBD undergoing maintenance therapy or after drug induction.

We conclude that one year after the adoption of the therapeutic approach, based on the dosage of IFX and ATI, the treatment could be maintained for most patients assessed. According to laboratory, endoscopic, and imaging examinations, there was not a significant relationship between IFX levels and the presence of ATI and the use of concomitant immunosuppressive drugs.

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### Authors' contribution

Kampa KC: data sampling, data analysis, writing of the paper. Ivantes CAP: data analysis. Petterle RR: statistical analysis. Pedroso MLA: data analysis and text review. Lourdes MR: data sampling

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Kampa KC, Loures MR, Ivantes CAP, Petterle RR, Pedroso MLA. A avaliação de níveis sérios de infliximabe favorece a manutenção do tratamento em pacientes com doença inflamatória intestinal. Arq Gastroenterol. 2023;60(1):48-56.

**RESUMO – Contexto –** A doença de Crohn e a colite ulcerativa são doenças crônicas nas quais existem desregulação do sistema imune da mucosa do trato gastrointestinal. Uma das terapias usadas no tratamento dessas doenças são as medicações biológicas, entre elas o Infliximabe. A monitorização do tratamento dos pacientes com Infliximabe é feita por exames complementares: calprotectina fecal, pesquisa de atividade inflamatória, exames endoscópicos e imagem. Utiliza-se, também a dosagem do nível sérico do Infliximabe e a pesquisa de anticorpos. **Objetivo –** Analisar uma população com doenças inflamatórias intestinais, em tratamento com Infliximabe, submetida a avaliação do nível sérico do Infliximabe e do anticorpo, além de possíveis fatores que possam alterar ou contribuir no tratamento. **Métodos –** Trata-se de estudo retrospectivo, transversal, realizado por meio da revisão dos prontuários dos pacientes com doença inflamatória intestinal, em um hospital sul-brasileiro, no período de junho de 2014 até julho de 2016, que foram submetidos a avaliação dos níveis séricos de Infliximabe e do anticorpo. **Resultados –** Foram incluídos 55 pacientes, submetidos a dosagem do Infliximabe e do anticorpo, totalizando 95 coletas sanguíneas. Destes, 55 realizaram uma primeira coleta, 30 tiveram uma segunda amostra coletada e 10 coletaram uma terceira vez. Vinte e nove pacientes eram do sexo feminino (52,7%) e vinte e seis do sexo masculino (43.2%). Quarenta e cinco (47,3%) casos tinham diagnóstico de doença de Crohn (81,8%) e 10 de colite ulcerativa (18,2%). Em relação ao nível sérico encontrou-se nível adequado em 30 coletas (31,57%), subterapêutico em 41 coletas (43,15%) e supraterapêutico em 24 coletas (25,26%). A prescrição foi otimizada em 40 (42,10%) casos, mantida em 31 (32,63%) pacientes, suspensa em 7 (7,60%) ou que o intervalo entre as infusões fosse aumentado (17,85%). Na análise geral, em 53 coletas (55,79%) a conduta foi definida em função exclusivamente da dosagem sérica do Infliximabe e/ou do anticorpo, já em relação, apenas a primeira coleta obteve-se 33 (60%) pacientes. Avaliando-se os pacientes um ano após, obteve-se: em 38 (69,09%) pacientes a conduta foi mantida com Infliximabe e, em 8 (14,54%) foi optado por troca de classe, em 2 (3,63%) foi optado por troca da medicação na mesma classe, em 3 (5,45%) pacientes a medicação foi suspensa e não foi substituída e, em 4 (7,27%), perdeu-se o seguimento. **Conclusão –** Não encontrou-se diferença entre os níveis de Infliximabe entre os grupos com ou sem imunossupressor, albumina sérica, velocidade de hemossedimentação, Calprotectina, Proteína C reativa, exames endoscópicos e exames de imagem. A conduta atual pode ser mantida em quase 70% dos pacientes. Concluindo, a dosagem do nível sérico e do anticorpo é ferramenta útil no acompanhamento dos pacientes em terapia de manutenção e após a indução de tratamento em pacientes com Doença Inflamatória Intestinal.

**Palavras-chave –** Doença de Crohn; colite ulcerativa; Infliximabe; anticorpo contra infliximabe; monitorização; terapia biológica.

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