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Importance of measuring levels of infliximab in patients treating inflammatory bowel disease in a Brazilian cohort

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ABSTRACT – **Background** – Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases. In such pathologies, there is an increased production of alpha tumor necrosis factor (TNF-α). Patients, in whom the conventional immunosuppressant treatment fails, require the use of immunobiological therapy, such as anti-TNF-α, a monoclonal antibody. infliximab is an anti-TNF-α drug, a chimerical immunoglobulin, with a murine component, which is responsible for the generation of immunogenicity against the drug and formation of anti-TNF-α antibodies. The presence of anti-drug antibodies may be responsible for adverse events and reduction of the drug's effectiveness. Patients with inflammatory bowel diseases undergoing therapy with biological medication, such as infliximab, can relapse overtime and this may not be translated into clinical symptoms. Thus, there is a need for a method to evaluate the efficacy of the drug, through the measurement of serum infliximab levels, as well as antibodies research. **Objective** – This study aimed to measure serum infliximab levels and anti-infliximab antibodies in patients with inflammatory bowel diseases post-induction phase and during maintenance therapy, and describe the therapeutic modifications that took place based on the serum levels results. **Methods** – It was a retrospective study, that included forty-five patients, with a total of 63 samples of infliximab measurement. **Results** – Twenty-one patients had an adequate infliximab serum level, 31 had subtherapeutic levels and 11 had supratherapeutic levels. Seven patients had their medication suspended due to therapeutic failure or high levels of antibodies to infliximab. **Conclusion** – In conclusion, only a third of the patients had adequate infliximab levels and 36% presented with subtherapeutic levels at the end of the induction phase. Therapy optimization occurred based in about 46% of the samples results, demonstrating the importance of having this tool to help the clinical handling of patients with inflammatory bowel diseases ongoing biologic therapy.

HEADINGS – Inflammatory bowel diseases, therapy. Crohn's disease. Ulcerative colitis. Infliximab. Tumor necrosis factor-alpha. Monoclonal antibodies, immunology.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD), that result from the deregulation of gastrointestinal tract mucous membrane's immune system, in patients genetically predisposed[19]. There is an increase in the production of alpha tumor necrosis factor (TNF-α) a proinflammatory cytokin, by the macrophages, monocytes, and T lymphocytes in the intestinal mucous membrane.

Patients who fail conventional immunosuppressant treatment need to receive immunobiological therapy, such as anti-TNF-α, a monoclonal antibody. This therapy is effective in inducing and maintaining remission in IBD individuals[19].

Infliximab (IFX) is an anti-TNF-α drug, a chimerical immunoglobulin IgG1 (75% human and 25% murine). The murine component is responsible for generating immunogenicity against the drug and formation of antibodies[14,15]. The presence of antibodies to infliximab (ATI) is responsible for the adverse events[18] and reduction of the drug's efficacy[15,25,27]. Factors that can also interfere with drug´s efficacy are accelerated clearance of the drug[9], body weight, concomitant use of other medications, type of disease and degree of inflammation[8,15,25].

CD is a complex condition, with a complex distribution. According to 2010 ECCO's consensus[2], we can classify it according to its extension in: 1) terminal ileitis; 2) colonic disease; 3) ileocolonic disease, and 4) upper gastrointestinal tract involvement. Another classification is based on its behavior: 1) non-stenosing and non-penetrating; 2) stenosing; 3) penetrating (with or without perineal impairment).

UC, on the other hand, may be classified by the Montreal criteria[7], according to the distribution of the disease, based on macroscopic colonic alterations: 1) proctitis: involvement limited to the rectum; 2) left colitis: distal to the splenic flexure; and 3) extensive colitis: it exceeds proximally the splenic flexure and includes pancolitis.

Patients with IBD undergoing biologic therapy, such as IFX, may have disease relapses many times, detected by endoscopic alterations and/or increased levels of inflammatory markers. However, frequently, relapses may not be translated into clinical symptoms[10,19]. A method for evaluating drug's efficacy is necessary, such as the serum level measurement of IFX, as well as antibody research[14,26]. This method can demonstrate low levels of IFX, with negative or low ATI in some patients, who might benefit from therapy optimization, by increasing medication's dose or decreasing administration intervals[11,23].

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The present study is one of the first Brazilian research regarding the dosage of IFX and ATI serum levels. Knowledge of those levels will decrease the unnecessary exposure of the patient to the drug. It will also allow adjustment of the dosage (increasing or decreasing) according to each case. This helps provide an individualized approach, more adequate to each patient.

METHODS

This is a transversal retrospective study, performed in patients of the IBD ambulatory of *Nossa Senhora das Graças Hospital*, from July 10, 2013 to April 30, 2015, based on the revision of patients' charts and dosage of IFX and ATI serum levels. All patients were undergoing maintenance therapy with IFX or concluding induction phase[8]. The induction phase involves the administration of 5 to 10 mg/kg of IFX in the following manner: the first dose in the week zero, the second dose in 2 weeks and the third, in the sixth week. Classically, maintenance therapy is performed every 8 weeks. The dosage of IFX and ATI levels after the induction phase was performed in the 14th or 22nd week.

The blood samples were collected immediately before the next infusion of the medication[1], stored at -20°C and finally sent to the *University Hospital Leuven*, in Belgium. The samples were analyzed by a method developed by the university, based on the *ELISA* (Enzyme Linked Immune Sorbent Assay) method[25,27]. The lower level of detection of IFX is higher or equal to 0.3 mcg/mL. In the cases where the IFX dosage was low, levels of ATI were given, classified into absence of ATI, low ATI level (<8 mcg/mL) and high ATI level (> or equal to 8 mcg/mL)[25]. The therapeutic IFX levels include values between 3 and 7 mcg/mL[21]. Above that, they are considered to be supratherapeutic, and below that, subtherapeutic.

Demografic data

The study included 63 samples collections for IFX dosages from 45 patients: 22 males and 23 females. Thirty-six patients were diagnosed as having CD and 9, as having UC. Individuals were between 17 and 67 years old, with an average of 39.5 years. The duration of the disease varied from 1 to 28 years, with an average of 9.3 years of diagnosis (Table 1).

TABLE 1. Population characteristics

	CD	UC
N	36	9
Sex		
Male	20	2
Female	16	7
Standard		
Small	5	
Ileocolonic	28	
Colon	3	
Pancolitis		8
Proctitis		1
Left colon		0
Duration of disease (years)	1 to 28	1 to 18

CD: Crohn's disease; UC: ulcerative recto colitis. Characteristics of the sample, division by sex, disease and classification.

The indication of IFX measurement was based in: disease control evaluation (39 samples, 61.9%); suspicion of medication failure or persistence of symptoms (13 samples, 20.63%); and after the end of induction phase (11 patients, 17.46%).

RESULTS

After the analysis of the IFX serum levels, the therapeutic approach was performed according to the decision of the practitioning doctor. The prescription was maintained in 17 (26.98%) cases, optimized according to the serum level in 22 (34.92%), optimized by clinical decision in 8 (12.69%), suspended in 7 (11.11%) patients (in 4 due to ATI presence and in 3 due to ineffectiveness of the drug); in 9 (14.28%) patients the interval between the doses was increased (Table 2). The optimization of treatment was varied, with an increase in the dosage from 5 mg/kg to 10 mg/kg or reduction of the administration interval, which varied from two to 4 weeks.

TABLE 2. Clinical management adopted in relation to the prescription of infliximab in patients with chronical intestinal inflammatory disease

Serum level	N (%)	Management
Therapeutic n: 21 (33.33%)	16 (76.19)	Maintained
	4 (19.04)	Optimized
	1 (4.76)	Suspended
Subtherapeutic n: 31 (49.20%)	26 (83.87)	Optimized
	5 (16.12)	Suspended
Supratherapeutic n:11 (17.46%)	8 (72.72)	Increased interval
	2(18.18)	Optimized
	1 (9.090)	Suspended

Among the patients with adequate serum level (n=21), one patient had the medication suspended due to persistence of symptoms and other four had the medication optimized for the same reason. Of the 16 patients who had their medication maintained with the same dosage and interval, 15 were clinically in remission and the measurement was done for control. There was a suspicion of treatment failure in one patient, but, with the result of adequate serum levels, the management was sustained.

Among the individuals with low levels (n=31) of IFX, five had the medication suspended, four due to high levels of ATI and one due to the persistence of symptoms; the other 26 had their medication optimized.

Of those with IFX levels above 7, regarded as supratherapeutic (n=11), one had his medication suspended due to clinical relapse and other two patients had a reduction of administration interval, because there was a suspicion of therapeutic failure. The remaining eight patients were clinically stable, so it was decided to increase the intervals of IFX infusion.

The reason for the suspension of the medication in seven patients was therapeutic failure or high levels of ATI (Table 3).

TABLE 3. Suspension of infliximab

IFX	Collection	Level of IFX (mcg/dL)	Level of ATI (mcg/dL)	Reason
Therapeutic	1	3.6	Undetectable	Symptoms
	2	<0.3	12.6	ATI
	3	<0.3	20	ATI
Subtherapeutic	4	<0.3	11.3	ATI
	5	<0.3	666	ATI
	6	<0.3	<0.5	Symptoms
Supratherapeutic	7	12.1	Undetectable	Symptoms

IFX: infliximab; ATI: antibodies to infliximab. Reasons for the suspension of IFX in seven patients, division according to the serum level of IFX.

In four of the eleven patients in which the collection was performed after conclusion of the induction phase (in the 14th or 22nd week), the level was already subtherapeutic (Table 4).

TABLE 4. Level of infliximab post-induction

Collection	Base Disease	Week of the Collection	Level of IFX (mcg/dL)	Level of ATI (mcg/dL)
1	CD	14	9.9	Undetectable
2	UC	14	10	Undetectable
3	UC	22	4.6	Undetectable
4	CD	22	6.4	Undetectable
5	CD	14	4.6	Undetectable
6	UC	14	3.6	Undetectable
7	CD	14	3.5	Undetectable
8	CD	14	<0.3	Undetectable
9	CD	14	2	Undetectable
10	CD	14	2.5	Undetectable
11	UC	14	0.8	Undetectable

CD: Crohn's disease; UC: ulcerative colitis; IFX: infliximab, ATI: antibodies to IFX. Serum level of 11 patients post-induction, showing that in 4 the level was subtherapeutic and in 2 supratherapeutic; only 5 patients had an adequate level of IFX.

All the patients had their ATI serum level measured, but due to the method technique adopted at the University Hospital Leuven, the quantification was only possible when the IFX levels were low. For this reason, the ATI were quantified in 14 samples of the 63 (22.22%). Of these, four patients had their medication suspended due to the high levels of ATI, 9 had their medication optimized and one had his medication optimized by clinical decision (Table 5).

Among the 63 collections, 22 (34.92%) showed low levels of IFX, besides undetectable levels of ATI.

In the general analysis, 29 samples (46.03%) defined the medical approach due solely to the serum levels of IFX and/or ATI.

DISCUSSION

Biologic drugs are widely used in clinical practice, including patients with IBD. There are many classes of biologicals. The anti-TNF is one of the main classes for treating IBD. Among them, the most prescribed are IFX, adalimumab and certolizumab.

TABLE 5. Level of anti-drug antibody

Conduct	Collection	Level of IFX (mcg/dL)	Level of ATI (mcg/dL)	Reason for the alteration
Optimized	1	<0.3	<0.5	Level of IFX
	2	<0.3	3.6	Level of IFX and ATI
	3	<0.3	<1	Level of IFX
	4	<0.3	0.5	Level of IFX
	5	<0.3	2.4	Level of IFX and ATI
	6	<0.3	<1	Level of IFX
	7	<0.3	<5	Level of IFX
	8	<0.3	<5	Level of IFX
	9	<0.3	<0.5	Level of IFX
	10	<0.3	<1	Level of IFX
Suspended	11	<0.3	12.6	ATI
	12	<0.3	>20	ATI
	13	<0.3	666	ATI
	14	<0.3	11.3	ATI

IFX: infliximab; ATI: antibodies to IFX. Level of ATI in the 14 patients who were given doses, showing the chosen conduct. Suspended in four patients due to high levels of ATI, optimized in 10 patients (9 due to low level of IFX and 1 by clinical decision).

The use of IFX in IBD started at the end of the 90's, initially for CD and later, for UC. Over the years, a loss of the response to this medication has been observed (loss of secondary response)[11]. It is estimated that within a year only about 50% of the patients will have maintenance of the remission[6,16,21]. Other studies estimate an annual loss of 10% in the response[23]. There are many mechanisms that generate loss of response, including the immunogenicity[9]. Overlapping of functional symptoms may simulate loss of response. Immunogenicity occurs in 10%-20% of individuals due to formation of antibodies against the anti-TNF drugs[1,3,16,26]. These antibodies are generally lgG type and connect to the reticulum endothelium system, accelerating the clearance of the drug and increasing the risk of loss of response and infusional reactions. One of the causes for antibody formation is the low serum level of the anti-TNF drug. This may happen due to inadequate optimization of the medication[4]. Functional symptoms may arise the suspicion of loss of response, leading to the suspension of the medication[12]. Functional symptoms include generally pain and diarrhea in the absence of active inflammation diagnosed by endoscopic examinations[4]. They are complex, many times clinically impossible to differentiate from organic ones. Other causes of loss of response are late complications such as stenosis, fistulas, neoplasia or infections (*Clostridium difficile* and cytomegalovirus), that produce symptoms and do not respond to biological therapy. There are strategies for monitoring activity of patients with IBD, such as dosage of fecal calprotectin[13] and the evaluation scores of diseases: *Crohn's Disease Activity Index* (CDAI) for CD[2]; and the Mayo, Truelove and Witt scores for UC[7].

There are two strategies for optimazing biological therapy: the proactive and the empirical strategies. The proactive consists of changing management according to the measurement of IFX and ATI serum levels. Empiric therapy consists of dosage modifying according to symptoms or exams alterations (radiologic, endoscopic or laboratory). This study showed that, from the total

of 63 collections performed, thirty-one (49.20%) approaches were modified based solely on IFX and ATI levels, which means that a proactive strategy was used. This is not much, considering it is a more cost effective strategy which causes less relapse episodes of the disease, compared to increasing the dosage in an empirical manner[4,16,26]. The TAXIT study[24] selected individuals in remission, and adjusted the IFX dosage according to its serum level found in the beginning of the study. Later, patients were randomized in two groups: one with an empirical conduct and the other with a proactive. After a year, the remission rates were similar in both groups. However, more patients in the empirical group needed a rescue therapy (17.3% against 5.5%). The TAXIT study suggests a reevaluation of the IFX dosage every 6 months. Other studies[4,26] showed that when using proactive therapy recurrence of disease and the rates of adverse effects to the infusion were smaller, and with less need for suspension of the medication; thus, we concluded that the IFX proactive therapy may have an important impact in relation to the length of maintenance of the therapy.

It is known that the scheduled therapy of IFX infusion (every 8 or 6 weeks)[1,16,22] decreases the rate of relapse of the disease, compared to the incidental administration, because patients respond better and suffer less complications, along with decreasing antibody formation[19,27]. The use of immunomodulators associated with biological therapy also reduces the loss of efficacy of the drug and decreases the risk of antibody formation[1,5,20].

This is one of the first Brazilian study with measurement of IFX and ATI serum level in IBD patients. In this study, only 33.33% of the samples had adequate IFX levels. The majority (66.66%) needed some kind of intervention. The main reason for the suspension of medication was the increased levels of ATI. The presence of 22% of ATI is consistent with other studies that show a formation of ATI between 5% and 21%[1,8,17].

Antibody formation is not the only reason for decreasing IFX therapeutic effects. Sometimes low levels of IFX are found, even in the absence of ATI[8,21]. One other explanation for it is the increased clearance of the drug, which promotes decreasing of clinical benefits of the medication. This research found 22 collections (34.92%) with low levels of IFX and undetectable levels of ATI. These patients had their therapy optimized.

Seventy-four percent of the collections led to some change in the treatment strategy. This reinforces the importance of this tool for guiding patients management undergoing biological therapy, for, in its absence, patients would be exposed to an ineffective or suboptimal treatment, along with the adverse effects of the composite, without a true clinical benefit.

Another important factor in maintaining the IFX therapeutic effect for as long as possible is that switching to another anti-TNF generally leads to a lower rate of clinical response[1].

Adequate IFX levels were found in 44% and 33.33%, subtherapeutic levels in 21% and 49.2% and supratherapeutic levels in 21% and 17.46% in the TAXIT study[3] and in this study, respectively.

One limitation of this study is related to it being retrospective, and for this reason presenting failures in data collection, such as problems with the writing of the patients' charts. Another limitation is the absence of a detailed description relating the clinical condition with the serum level found at the moment of the collection. We decided to perform a case-by-case description, a correlation of IFX and ATI serum levels with the medical approach.

As a conclusion, the dosage of IFX and ATI serum levels is a useful tool for guiding the follow up of patients post-induction and maintenance therapy, for it may identify inadequate levels, both insufficient or elevated, permitting the optimization of IFX administrations, allowing a better chance to obtain a successful therapy with less risk of adverse events.

Authors' contributions

Kampa KC: data collection, survey execution and text writing. Morsoletto DBG: data collection. Loures MR: data collection, text revision. Pissaia Junior A: data collection. Nones RB: data collection, text revision. Ivantes CAP: text revision and research supervision.

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RESUMO – **Conteúdo** – Doença de Crohn e retocolite ulcerativa são doenças inflamatórias intestinais crônicas. Nelas, ocorre aumento da produção de fator de necrose tumoral alfa (TNF-α). Pacientes que falham no tratamento convencional imunossupressor, requerem uso de terapia imunobiológica, que são anticorpos monoclonais, principalmente os anti-TNF-α. O infliximabe é uma droga anti-TNF-α, uma imunoglobulina quimérica, com componente murino. Este é responsável pela imunogenicidade da droga e a formação de anticorpos. Presença de anticorpos antidroga pode ser responsável pelos eventos adversos e redução da eficácia da droga. Pacientes com doenças inflamatórias intestinais, em terapia imunossupressora com medicação biológica como o infliximabe, podem ter recaída da doença e muitas vezes isso não se relaciona com a sintomatologia do paciente. Por isso há a necessidade de um método de avaliação do efeito da droga como a dosagem do nivel sérico do infliximabe, bem como da pesquisa de anticorpos. **Objetivo** – O estudo tem como objetivo conhecer os níveis séricos do infliximabe e dos anticorpos anti-infliximabe em pacientes com doença inflamatória intestinal em terapia de manutenção ou pós-indução e descrever as condutas terapêuticas que foram modificadas em função dos níveis séricos de infliximabe e anticorpos para infliximabe. **Métodos** – Trata-se de estudo restrospectivo, com análise da dosagem dos níveis séricos de infliximabe e anticorpos para infliximabe. Foram incluídos 45 pacientes, num total de 63 coletas de dosagem de infliximabe. **Resultados** – Vinte e um paciente estavam com o nível sérico de infliximabe adequado, níveis subterapêuticos em 31 pacientes e níveis supraterapêuticos em 11 pacientes. Sete pacientes tiveram a medicação suspensa por falha terapêutica ou altos níveis de anticorpos para infliximabe. **Conclusão** – Apenas um terço dos pacientes apresentavam níveis adequados de infliximabe e 36% dos pacientes apresentavam níveis subterapêuticos ao término da indução. Em cerca de 46% das amostras a conduta adotada se baseou nos níveis de infliximabe e anticorpos para infliximabe demonstrando a importância de se ter esta ferramenta para auxílio no manejo clínico dos pacientes portadores de doenças inflamatórias intestinais em terapia biológica.

DESCRITORES – Doenças inflamatórias intestinais, terapia. Doença de Crohn. Colite ulcerativa. Infliximab. Fator de necrose tumoral alfa. Anticorpos monoclonais, imunologia.

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