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Comparative analysis of adverse events between infliximab and adalimumab in Crohn's disease management: a Brazilian single-centre experience

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ABSTRACT

Introduction: Data is scarce regarding adverse events (AE) of biological therapy used in the management of Crohn's Disease (CD) among Brazilian patients.

Objectives: To analyse AE prevalence and profile in patients with CD treated with Infliximab (IFX) or Adalimumab (ADA) and to verify whether there are differences between the two drugs.

Method: Retrospective observational single-centre study of CD patients on biological therapy. **Variables analysed:** Demographic data, Montreal classification, biological agent administered, treatment duration, presence and type of AE and the need for treatment interruption. **Results:** Forty-nine patients were analysed, 25 treated with ADA and 24 with IFX. The groups were homogeneous in relation to the variables studied. The average follow-up period for the group treated with ADA was 19.3 months and 21.8 months for the IFX group ($p = 0.585$). Overall, 40% ($n = 10$) of patients taking ADA had AE compared with 50% ($n = 12$) of IFX users ($p = 0.571$). There was a tendency towards higher incidence of cutaneous and infusion reactions in the IFX group and higher incidence of infections in the ADA treated group, although without significant difference.

Conclusions: No difference was found in the AE prevalence and profile between ADA and IFX CD patients in the population studied.

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Análise comparativa dos eventos adversos entre Infiximabe e Adalimumabe no tratamento da doença de Crohn: experiência em um centro brasileiro

R E S U M O

Palavras-chave:

Doença de Crohn

Fator de necrose tumoral-alfa

Segurança

Introdução: Há poucos dados sobre os eventos adversos (EA) da terapia biológica usada no tratamento da doença de Crohn (DC) entre os pacientes brasileiros.

Objetivos: Analisar a prevalência dos EA e o perfil dos pacientes com DC tratados com Infiximabe (IFX) ou Adalimumabe (ADA) e verificar se há diferenças entre esses dois fármacos. *Método:* Estudo observacional e retrospectivo de pacientes com DC em terapia biológica, realizado em centro único. As variáveis analisadas foram: dados demográficos, classificação de Montreal, agente biológico administrado, duração do tratamento, presença e tipo de EA e necessidade de interrupção do tratamento.

Resultados: Quarenta e nove pacientes foram analisados, 25 tratados com ADA e 24 com IFX. Os grupos eram homogêneos em relação às variáveis estudadas. O período médio de acompanhamento foi de 19,3 meses para o grupo tratado com ADA e de 21,8 meses para o grupo tratado com IFX ($p = 0,585$). No total, 40% dos pacientes ($n = 10$) que receberam ADA tiveram AE, em comparação com 50% dos pacientes ($n = 12$) que receberam IFX ($p = 0,571$). Houve uma maior incidência de reação cutânea e à infusão no grupo IFX e de infecções no grupo ADA, embora sem diferença significativa.

Conclusão: Não houve diferença na prevalência de EA e no perfil dos pacientes com DC que receberam ADA e IFX.

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Introduction

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) remain an important challenge for physicians and patients with regard to treatment and clinical follow-up. Recent therapeutic progress has been achieved in the management of IBD, whereby biological therapy is currently one of the most studied forms of treatment among these patients.¹

CD is a chronic inflammatory condition of the gastrointestinal tract which is characterized by periods of remission and relapse, progressing over the years to complications such as stenosis, fistulas or abscesses.¹ Its pathogenesis is not yet totally understood. Tumour necrosis factor-alpha (TNF- α) is an important cytokine involved in the development of CD and it plays an important role in the genesis and sustainability of the inflammatory process in the inflamed areas.^{3,4,5}

Considering IBD physiopathology, whereby the pro-inflammatory factors are directly involved in the genesis of inflammation, therapeutic options have been developed aiming the blockage of TNF- α in order to delay the progression of the disease and its complications.^{4,5}

Two agents are available in Brazil to inhibit TNF- α in the treatment of CD. Infiximab (IFX) [Remicade®, Centocor, USA], a chimeric monoclonal antibody containing 25% of murine protein and administered intravenously, has been authorized for CD patients since the year 2000. It is the most studied drug regarding biological therapy in CD. Clinical trials have demonstrated the efficacy in induction therapy and maintenance of remission of IFX in patients with moderate to severe disease, including those with fistulas.^{1,6,7,8} IFX has

also been approved for children with CD and for the management of UC.^{6,8,9}

Adalimumab (ADA) [Humira®; Abbott Laboratories, Abbott Park, USA] is a 100% human monoclonal antibody administered subcutaneously and its use has been authorized in Brazil since 2007. ADA is also indicated for induction and maintaining remission in moderate to severe refractory CD. Its action has also been proven in the event of IFX failure.^{2,3,10} ADA is currently not approved for the management of children with CD and it was recently approved for the management of UC in the United States and Europe.

The efficacy of these two anti-TNF agents has been exhaustively documented in the literature by important randomized pivotal studies.^{3,6} Remission rates following induction with varying periods of maintenance are similar between the two drugs. Some authors consider these drugs to be similar in various aspects and question the theory of a TNF- α inhibitor class effect.¹¹

Likewise, the safety profile and the adverse events (AE) of IFX and ADA appear to be similar. Both drugs have the potential to cause cutaneous reactions, opportunistic infections, abscesses, respiratory tract infections and rare conditions such as optic neuritis, multiple sclerosis and lupus-like reactions.^{1,12} Some AE are characteristic of the drug application, such as reactions at the subcutaneous injection site (ADA) and infusion reactions of anaphylactic and immunological origin (IFX). AE can vary between simpler conditions, such as sinusitis and urinary infections, to more important effects, such as severe infections and sepsis leading to death.^{2,6,12}

Due to the lack of solid studies of the efficacy and safety of anti-TNF- α agents in Brazilian patients with CD, more research is necessary in order to adequately elucidate the prevalence and profile of AE in this population in reference

centres. Therefore, real-life information found in everyday clinical practice in CD management can be applied to improve the knowledge in our field.

Objectives

The primary objectives of this study was both to analyse the prevalence and profile of AE in patients with CD treated with IFX or ADA, from a single centre cohort of one IBD reference centre from the Southern Region of Brazil, as well as to verify whether there are significant differences between the two drugs.

The secondary objectives were to analyse demographic data, follow-up period with the agents and the presence of treatment interruption due to AE.

Method

This study's research project obtained prior approval from the Human Research Ethics Committee of the Pontifícia Universidade Católica of Paraná (CEP – PUCPR) under reference number 0005345/11.

It was a retrospective, longitudinal and observational study with CD patients from a single IBD reference centre from the South of Brazil. All patients from a CD cohort that were treated with any biological agent (IFX or ADA) at any stage of their management were included in the study, over 18 years old, in the period between January 2002 and December 2011. Patients with UC, indeterminate IBD and those who lost follow-up after the induction of clinical remission were excluded.

Data were collected by electronic chart review and documented in accordance with a previously established specific protocol. Once the data had been compiled it was tabulated to enable subsequent analysis and evaluation.

The following variables were analysed: demographic data (gender and mean age), disease presentation and location according to the Montreal classification, concomitant use of immunosuppressive drugs, the biological agent used, treatment duration, presence of AE, type of event observed and the need for treatment interruption.

The patients were allocated into two groups according to the biological agent, either IFX or ADA. A comparison was made of the data on the prevalence and type of AE in the two groups. The study's hypothesis was that there would be no difference between the AE prevalence and profile observed in the two groups.

The AE of pain at the subcutaneous injection site (ADA) or venous puncture in the case of IFX administration were excluded from the analysis, as pain is a subjective characteristic and the vast majority of patients report this consequence of drug administration. In the IFX group, the occurrence of infusion reaction was considered to be an adverse effect, this being a characteristic unique to this drug owing to its pharmacological features.

Sample size calculation was not performed in this study. Rather, convenience sampling was used according to the real number of patients in the cohort previously mentioned. The results obtained through the study were described in terms of

averages, minimum values, maximum values and standard deviations (quantitative variables) or in terms of frequencies and percentages (qualitative variables). Fisher's exact test or the Chi-square test were used in the evaluation of the association between treatment and qualitative variables. The Student's t test for independent samples or the Mann-Whitney non-parametric test were used when comparing treatment in relation to quantitative variables. P values < 0.05 indicated statistical significance. The data were analysed using the Statistica v.8.0 software.

Results

A total of 49 patients with CD were included in the analysis, 25 of whom were treated with ADA and the remaining 24 were treated with IFX. There was no statistical difference between the groups regarding mean age and gender. Similarly, when analysing the CD phenotype characteristics in relation to the Montreal classification (age of diagnosis, disease location and the phenotype of its presentation) once again there was no statistical difference between the groups. This absence of difference between the groups from the statistical point of view was also observed in relation to the following variables: presence of perianal disease, concomitant immunosuppressive drugs and follow-up period. The groups were therefore considered to be homogeneous and comparable for the purposes of this analysis. This data can be found in detail in Table 1.

Regarding the incidence of AE observed in the groups, these occurred in 40% of patients with CD treated with ADA (n = 10 of the 25 patients) and in 50% of those treated with IFX (n = 12 of the 24 patients) (p = 0.571). In terms of the absolute number of events observed, 14 AE were observed in 10 patients in the group treated with ADA, and 12 events in 12 patients treated with IFX (p = 0.911). This means that some patients had more than one AE during treatment. Based on these results, no significant difference was found in the rate of adverse events in the two groups (Table 2).

Table 1 – Baseline characteristics of the patients. There was no statistical difference between the groups, considered to be homogeneous.

	ADA (n = 25)	IFX (n = 24)	p value
Mean age (years)	37.5 (18-80) SD = 14.1	41.3 (19-70) SD = 14.6	0.352
Male gender	13 (52)	14 (58.33)	0.776
Female gender	12 (48)	10 (41.67)	
A1	6 (24)	5 (20.83)	0.138
A2	14 (56)	8 (33.33)	
A3	5 (20)	11 (45.83)	
L1	4 (16)	3 (12.5)	0.897
L2	11 (44)	10 (41.67)	
L3	10 (40)	11 (45.83)	
L4	0 (0)	0 (0)	—
B1	4 (16)	7 (29.17)	0.269
B2	4 (16)	1 (4.17)	
B3	17 (68)	16 (66.67)	
Perianal disease	19 (76)	17 (70.83)	0.754
Concomitant immunosuppressants	22 (88)	21 (87.5)	1.000

Table 2 – Prevalence of AE in the two groups of patients. Absence of statistical difference in relation to frequency (p = 0.571).

Adverse events: n (%)	ADA (n = 25)	IFX (n = 24)	Total	p value
No	15 (60)	12 (50)	27	p = 0.571
Yes	10 (40)	12 (50)	22	
Total	25	24	49	

The profile of the AE is demonstrated in Table 3. A tendency of greater occurrence of cutaneous and infusion reactions was observed in the IFX group. A greater tendency of infectious AE, such as sinusitis, herpes simplex and herpes zoster was observed in the ADA group (Table 3). Nevertheless, there was no statistical difference in relation to these data.

Figs. 1, 2, 3 and 4 show some of the AE found in the patients included in the study, with detailed subtitles.

In this study, some cases of treatment interruption due to AE were observed. In the IFX group, 8 of the 12 patients with AE had to interrupt their biological treatment. In the group of ADA, 4 of the 10 patients had AE that lead to treatment interruption. There was no statistical difference between the groups in relation to this variable (Fig. 5).

Discussion

The efficacy of anti-TNF agents in the treatment of CD is well-known and clearly demonstrated in the literature. Various randomized trials have been performed showing the benefits of this treatment in the remission of the disease.^{3,6} Nevertheless, there is significant concern regarding the safety of the administration of biological agents to treat CD patients. The safety profile of these drugs has been described in various studies which have demonstrated the occurrence of common events such as headache, infections and infusion reactions,

Table 3 – Profile of the AE found in the two groups of patients. Individually, for each type of event, there was no significant difference between the groups.

Adverse effect (n/%)	ADA (n = 25)	IFX (n = 24)	p value
Cutaneous reactions	2 (8)	4 (16.7)	0.367
Sinusitis	3 (12.5)	1 (4.17)	0.609
Arthralgia	2 (8)	1 (4.17)	1.000
Severe infusion reaction	0 (0)	3 (12.5)	0.110
Alopecia	2 (8)	0 (0)	0.490
Slight infusion reactions	0 (0)	2 (8.33)	0.235
Headache	1 (4)	0 (0)	1.000
Herpes simplex	1 (4)	0 (0)	1.000
Herpes zoster	1(4)	0 (0)	1.000
Perianal HPV	0 (0)	1 (4.17)	0.490
Ungueal inflammation	1 (4)	0 (0)	1.000
Leukocytoclastic vasculitis	1(4)	0 (0)	1.000
Mean follow-up period (months)	19.3 (3-39)	21.8 (2-81)	0.585

as well as other situations, such as opportunistic infections, lymphomas, demyelinating disease and lupus-like reactions.²

The two groups of patients included in this study were considered to be homogeneous. The median age of patients receiving IFX was 41.3 years, this being similar to that found in the literature in two studies with large patient samples, in which the median ages were 35 and 37 years.^{8,13} With regard to the demographic profile of the patients treated with ADA,



Fig. 1 – Leukocytoclastic vasculitis after 3 years of ADA treatment.



Fig. 2 – Herpes zoster infection during ADA treatment in a patient with severe CD and short bowel syndrome.



Fig. 3 – Facial cutaneous reaction an IFX-treated patient.



Fig. 4 – Hand cutaneous reaction during IFX treatment.

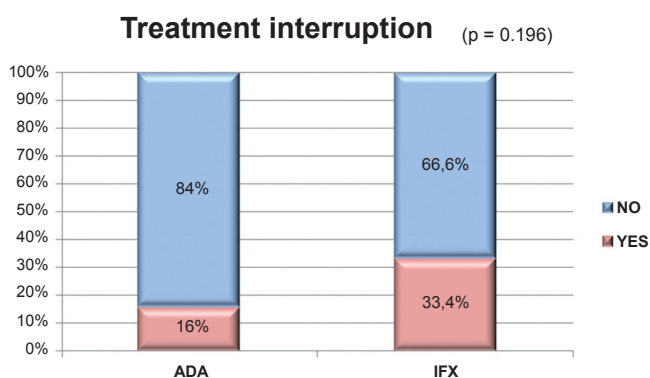


Fig. 5 – Results regarding treatment interruption rates owing to AE. No statistical difference between the groups.

the median age found in this study, 37.5 years, is also similar to that found in pivotal studies with the same drug (37.1 and 38.3 years).^{2,3} In both groups of our study, there was also predominance of the fistulizing form of CD, which can be explained by the fact that fistulas are one of the main indications for biological therapy, in addition to the bias caused by the reference centre in question being located in a colorectal surgery unit. The duration of follow-up, which is an important variable in retrospective comparisons between treatments, was also similar, with no significant statistical difference, and was greater than 18 months in both groups.

The administration of concomitant immunosuppressive drugs with anti-TNF agents was expressive in this sample. Approximately 88% of patients under ADA treatment and 87.5% of those receiving IFX were also exposed to some type of immunomodulators during their treatment. Controversy exists regarding this issue as there is scarce evidence to support the combined use of ADA and immunosuppressive drugs in randomized studies. In the literature, the concomitant administration of these drugs in the treatment of inflammatory bowel diseases is also very frequent. In a randomized study published in 2002, 51% of patients used some type of corticosteroid, 50% were on 5-aminosalicylates, 25% were exposed to 6-mercaptopurine or azathioprine and 4% used methotrexate, concur-

rently with IFX. This data demonstrates that in the past the concept of combining biologics with immunosuppressive agents had not been consolidated, judging by the low number of patients taking the two drugs concurrently. The numbers in this study are higher with regard to the use of combination therapy (greater than 85%). This can be explained by the more recent global tendency of using this treatment strategy, data that were consolidated with the publication of the SONIC study in 2010.^{6,13} Whether this combination may increase the rate of side effects has yet to be elucidated.

The occurrence of AE in patients under ADA treatment is documented in the literature in the form of opportunistic infections, such as oral candidiasis, rare lupus-like reactions, demyelinating disorders such as multiple sclerosis and optic neuritis, and congestive heart failure induced by this drug. Abscesses are the most serious form of infection, followed by gastrointestinal and pulmonary infections. Nevertheless, herpes zoster infection is also reported.²

The incidence of malignancies, such as lymphomas, despite not being clearly established, may be present in some rare cases. It is not clear whether the occurrence of neoplasms is associated with the biological agent *per se* or with the concomitant use of immunosuppressive agents. There were no neoplasms in the cases described in our series.

In the group using ADA in this sample, although the number of patients was reduced, greater occurrence of infectious adverse events was observed, whereby 12.5% of patients had sinusitis and 8% had herpes simplex and herpes zoster infections (Table 3). The patients included in the CHARM study³ had adverse effects in 59.4% of the cases (507/854) during the maintenance period, compared with 40% (10/25) in our group. It must be emphasized that in the above mentioned randomized study, pain at the subcutaneous injection site was included as an adverse effect and this may explain the higher incidence of events considered to be adverse.³

With regard to IFX, some adverse effects can be explained by the formation of antibodies against the drug (anti-IFX antibodies), leading to acute or delayed infusion reactions. Respiratory tract infections of variable severity can also occur with the administration of this drug. In some cases, more severe infectious conditions, such as fatal sepsis, pneumonia, viral infections and abdominal abscesses are described. The use of IFX by patients with congestive heart failure is accompanied by a risk of worsened functional classification. Although other manifestations such as optic neuritis, multiple sclerosis and lupus-like reactions are reported, they are rare.¹ The presence of anti-IFX antibodies or IFX serum levels were not assessed in this study.

Overall, 50% (12/24) of the patients in this study under IFX therapy presented some type of AE: 16.7% had some type of cutaneous lesion, 12.5% had a severe infusion reaction and 8.3% had slight infusion reaction. Other studies in the literature have already demonstrated the significant incidence of infusion reactions, as occurred in this study. In the ACCENT II trial,⁸ 16% of patients had infusion reactions when submitted to IFX therapy, this percentage being close to that found in the case series in our study.

Tuberculosis reactivation during treatment with ADA or IFX is described in the literature. None of the patients in this series had this adverse effect. All of them began biological therapy after rigorous PPD testing and chest x-rays, as well as sequenc-

ing tests when necessary. It is known that even when taking these precautions, cases of latent tuberculosis can manifest themselves, although this did not occur with the patients in this study. No deaths occurred in this case series.

The ADA and IFX efficacy and safety profiles appear to be similar in relation to experiences found in the literature. It must be emphasized that comparative head to head prospective studies with the two drugs have not been published, thus partially limiting this affirmation. As such a question arises as to the possible existence of a class effect between TNF-alpha inhibitors, not just in terms of safety but also in relation to efficacy.¹¹ This question is equally controversial in the international literature. The results of this study present a tendency towards similarity in the adverse events found with both drugs.

We are aware that this study has significant limitations. In addition to its methodological design, such as the small number of patients in the sample and being a retrospective study capturing data by reviewing patients' medical records, there are also the limitations of the relatively short average period of follow-up of the patients analysed (less than 2 years for both groups). Another limitation that can be taken into consideration relates to the period analysed by the study which includes patients treated for more than 9 years. Treatment using biological agents has evolved in recent years and the form of treatment used at the beginning of the millennium is a little different to the form currently used. This may have caused bias in the results, mainly due to the more recent tendency of using combination therapy.

Conclusions

Secondary adverse effects to anti-TNF therapy were found in 40% of the patients treated with ADA and in 50% of those treated with IFX, with no significant statistical difference. With regard to the profile of the events found, there was a tendency of greater incidence of cutaneous and infusion reactions in the group treated with IFX and a tendency of greater incidence of infections in the group treated with ADA. The patients' demographic data were similar to those described in the literature. This is one of the first Brazilian experiences published containing data related to the safety profile in patients with CD treated with biological therapy.

Conflict of interest

Paulo Gustavo Kotze is a speaker and consultant for **Astrazeneca**, **Takeda**, **Janssen** and **Abbott** laboratories. Lorete Maria da Silva Kotze and Claudio Saddy Rodrigues Coy are speakers for **Abbott** laboratories.

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