ORIGINAL ARTICLE

Safety profile and side effects of infliximab and adalimumab in inflammatory bowel disease at a referral center in northeastern Brazil

Perfil de segurança e efeitos colaterais do infliximabe e adalimumabe na doença inflamatória intestinal em um centro de referência no nordeste do Brasil

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RESUMO

Introduction: Anti-tumor necrosis factor-alpha agents (Anti-TNF-alpha) are an effective treatment option in patients with moderate and severe inflammatory bowel disease (IBD). **Objectives:** To evaluate safety profile of infliximab (IFX) and adalilumab (ADA) in IBD patients over a 10-year period at a referral center in Northeastern Brazil. **Methodology:** The medical records of 123 patients, of whom 104 (84.5%) had Crohn's disease and 19 (15.4%) had ulcerative colitis, were reviewed for side effects associated with the use of IFX (n=83) and ADA (n=40). **Results:** Thirty-one patients (25%) experienced side effects (IFX n=21; ADA n=10) (p=0.971), 15 (48%) of which were severe (IFX n=10; ADA n=5) (p=0.942). Acute reactions occurred in 9 patients (7.3%), infections in 13 (10%), malignancies in 3 (2,4%), psoriasis in 4 (3,2%), in addition to 3 deaths (2,4%). **Conclusion:** The frequency of side effects was similar for IFX and ADA. Both drugs are safe in the treatment of IBD, but careful screening and monitoring are necessary to identify and follow patients at risk of severe side effects.

Palavras-chave: Inflammatory bowel diseases. Infliximab. Adalimumab. Safety.

ABSTRACT

Introdução: Os agentes anti-fator de necrose tumoral alfa (anti-TNF-alfa) são uma opção de tratamento eficaz em pacientes com doença inflamatória intestinal moderada e grave (DII). **Objetivos:** Avaliar o perfil de segurança do infliximabe (IFX) e do adalilumabe (ADA) em pacientes com DII durante um período de 10 anos em um centro de referência no Nordeste do Brasil. **Metodologia:** Os prontuários de 123 pacientes, dos quais 104 (84,5%) tinham doença de Crohn e 19 (15,4%) retocolite ulcerativa, foram revisados para efeitos colaterais associados ao uso de IFX (n = 83) e ADA (n = 40). **Resultados:** Trinta e um pacientes (25%) apresentaram efeitos colaterais (IFX n = 21; ADA n = 10) (p = 0,971), 15 (48%) dos quais foram graves (IFX n = 10; ADA n = 5) (p = 0,942). Reações agudas ocorreram em 9 pacientes (7,3%), infecções em 13 (10%), neoplasias em 3 (2,4%), psoríase em 4 (3,2%), além de 3 óbitos (2,4%). **Conclusão:** A frequência dos efeitos colaterais foi semelhante para IFX e ADA. Ambas as drogas são seguras no tratamento da DII, mas a triagem e o monitoramento cuidadosos são necessários para identificar e acompanhar os pacientes com risco de efeitos colaterais graves.

Keywords: Doenças inflamatórias intestinais. Infliximab. Adalimumab. Segurança.

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INTRODUCTION

Immunobiological (IB) agents are indicated for patients with moderate to severe inflammatory bowel disease (IBD) and inadequate response or intolerance to conventional therapies. The earliest agents to be tested were tumor necrosis factor (TNF) inhibitors, such as infliximab (IFX) and adalimumab (ADA). The former is an endovenous chimeric monoclonal antibody with a 75/25 human-to-animal protein structure; the latter is a more recently approved fully human monoclonal antibody for subcutaneaos administration.[1,2]

Complex and multifactorial, the pathogenesis of IBD is strongly associated with excess TNF production. Anti-TNF-alpha agents inhibit this inflammatory mechanism and have been shown to successfully induce clinical remission of IBD.[3,4]

The main side effects of anti-TNF-alpha agents are allergic and infusional reactions, such as the emergence or reactivation of infections.[5] Toxicity is class-specific; thus, IFX and ADA are considered to have similar safety profiles, except for infusional adverse events.[6]

Several studies have shown that anti-TNF-alpha agents have acceptable safety profiles in both premarketing and large clinical trials. However, few studies on safety have been conducted in developing countries and the follow-up period is short in most of the studies.[7] Socioeconomic factors, as reflected in high prevalences of malnutrition and tuberculosis and in limited access to public health care, may play a role in the incidence of side effects of anti-TNF-alpha agents. In Brazil, a study carried out in the southern region of the country and published in 2017, showed a high incidence of adverse events and did not show significant differences between IFX and ADA.[8] Thus, in this study we evaluated the long-term safety profile of infliximab (IFX) and adalilumab (ADA) in IBD patients over a 10-year period at a referral center in Northeastern Brazil.

MATERIALS AND METHODS

The study was based on a retrospective cohort of IBD patients treated with IFX or ADA at an IBD referral outpatient service in Fortaleza Ceará, Northeastern Brazil (Hospital Universitário Walter Cantídio) between January 2008 and December 2018. The center serves populations through the Brazilian Unified Health Care System (SUS). IBD was diagnosed based on clinical, radiological, endoscopic and histological findings and categorized according to the Montreal Classification.[1]

The logs of the hospital dispensary were used to identify IBD patients receiving IFX or ADA during the study period. Patient information was then retrieved from medical records and, when necessary, completed through interviews. The following individual variables were systematically collected and tabulated: age, sex, diagnosis, comorbidities, time of disease, concomitant medication, follow-up, clinical and endoscopic response to IFX or ADA, and side effects. As for the latter, the time of onset, resolution, severity, outcome and association with IFX or ADA were registered.

Acute infusional reactions were defined as adverse effects occurring during or within one hour of the infusion. Drug-induced lupus (DIL) was defined as one or more symptoms (muscle and joint pain, swelling, flu-like syptoms, fever) associated with antinuclear antibodies and double-stranded DNA or anti-histone antibodies.[7]

Potential adverse events included any severe and/or opportunisitic infections, cancer or dysplasia, autoimmune diseases (infusional reactions, DIL, demyelinating disease), cardiovascular complications, and death.[7]

Treatment and preventive measures with IFX (Remicade; Centocor Inc., Malvern, PA) followed the guidelines proposed by scientific committees. The patients were shown by the nursing team how to self-administer ADA s.c. and instructed to seek emergency care and contact our outpatient team in the event of acute reactions. During outpatient follow-up, instructions were recapitulated and all TNF inhibitor-related side effects were registered.

Ethical considerations

The study was designed and conducted in accordance with the tenets of the 2008 Helsinki declaration, and the protocol was approved by our institutional research ethics committee (Hospital Universitário Walter Cantídio, Universidade Federal do Ceará) and filed under entry 3.168.019.

Statistical analysis

The software IBM SPSS Statistics v. 21.0 (IBM Corp, Armonk, NY, EUA) was used in all analyses. Categorical variables were expressed as absolute (n) and relative (%) frequencies. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables, when appropriate. Mean value (standard deviation) was used to describe normally distributed variables. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

The cohort consisted of 123 IBD patients treated with IFX (n=83; 67.5%) or ADA (n=40; 32.5%). The female sex was predominant (n=68, 55.3% vs. n=55, 44.7%), the average age was 39.2 years (range: 15-79), and the average time of disease was 9.45 years. Crohn's disease (CD) and ulcerative colitis (UC) were diagnosed in 104 (84.5%) and 19 (15.4%) patients, respectively. CD was located in the terminal ileum (n=45; 43.3%), the ileocolonic segment (n=39; 37.5%) or the colon (n=20; 19.2%). Over half the CD patients (n=54; 52%) had fistulizing disease. UC was classified as left colitis (n=9; 47.4%), pancolitis (n=8; 42.1%) or distal colitis (n=2; 10.5%).

Treatment with IB agents was indicated due to inadequate response to conventional therapies (n=80; 65%), severe fistulizing disease (n=8; 6.5%), or both (n=35; 28.5%). The

average follow-up of was 45.18 months. Two patients in the IFX group stopped treatment after one month due to the emergence of psoriasis and miliary tuberculosis. Two patients in the ADA group discontinued treatment after one month and two months, respectively, due to recurring episodes of itching and skin rash. In addition to TNF inhibitors, the patients received corticoids (n=8; 6.5%), immunosuppressants (n=72; 58.5%), corticoids and immunosuppressants (n=24; 19.5%), or neither (n=19; 15.5%) (Table 1). One fourth of the cohort (31/123) experienced adverse events, regardless of the TNF inhibitor (IFX 21/83; ADA 10/40). IFX was associated with acute reactions (5 skin rash/itching; 1 respiratory discomfort), 9 infections (2 urinary infections, 3 sepsis, one of which fatal), 1 pleural tuberculosis, 2 miliary tuberculosis (one of which fatal), 1 herpes zoster, 3 psoriasis, 1 drug-induced lupus, 1 colon lymphoma, and 1 colon adenocarcinoma. ADA was associated with 3 acute reactions (2 skin rash/itching;1 respiratory discomfort), 4 infections (1 fatal sepsis;1 urinary infection;1 liver abscess;1 systemic candidiasis), 1 severe neutropenia, 1 psoriasis, and 1 chronic myeloid leukemia (Table 2).

Thus, 15 severe adverse reactions were observed in our cohort (9 using IFX, 5 ADA p=0.804, including respiratory discomfort, sepsis, liver abscess, pleural and milliary tuberculosis, systemic candidiasis, colon adenocarcinoma, colon lymphoma, chronic myeloid leukemia, and drug-induced lupus (Table 3).

Table 1. Clinical characteristics of a Northeast Brazilian cohort of 123 patients treated with TNF inhibitors for inflammatory bowel disease (IBD).

Variables	n %
Female/male	sex 68 (55.3%) / 55 (44.7%)
Age	Mean: 39.2 years; range: 15-79
Years Time of disease	Mean: 9.45 years
IBD subtype	
Crohn's disease (CD)	104 (84.5%)
Ulcerativecolitis (UC)	19 (15.4%)
Location of CD	
Terminal ileum	45 (43.3%)
Ileocolonic segment	39 (37.5%)
Colon	20 (19.2%)
Fistulizing	54 (52%)
Location of UC	
Left	9 (47.4%)
Distal	2 (10.5 %)
Pancolitis	8 (42.1%)
Indication for immunobiological therapy	
Refractary disease	80 (65.0 %)
Fistulizing disease	8 (6.5%)
Both	35 (28.4 %)
TNF inhibitor	
Infliximab (IFX)	83 (67.5%)
Adalimumab (ADA)	40 (32.5%)
Concomitant medication	
Corticoids	8 (6.5%)
Immunosuppressants	72(58.5%)
Both	24 (19.5%)
None	19 (15.4%)

Table 2. Side effects associated with the use of infliximab (IFX) and adalimumab (ADA) in a Northeast Brazilian cohort of 123 patients with inflammatory bowel disease.

	IFX(n=83)	ADA(n=40)	P
	n (%)	n (%)	
Side effects (n=31) 25%	21 (25)	10 (25)	0,971
Acute reactions (n=9)(7,3%)	6 (7.2)	3 (7.5)	0,956
Skin rash and itching (n=7)	5 (6.0)	2 (5)	
Respiratory discomfort (n=2)	1 (1.2)	1 (2.5)	
Infections (n=13) 10%	9 (10.8)	4 (10)	0,886
Urinary infection (n=3)	2 (2.4)	1 (2.5)	
Sepsis (n=4)	3 (3.6)	1 (2.5)	
Liver abscess (n=1)	-	1 (2.5)	
Systemic candidiasis (n=1)	-	1 (2.5)	
Herpes zoster (n=1)	1 (1.2)	-	
Pleural tuberculosis (n=1)	1 (1.2)	-	
Miliary tuberculosis (n=1)	1 (1.2)	-	
Other (n=9)	6 (7.2)	3 (7.5)	0,956
Psoriasis (n=4)	3 (3.6)	1 (2.5)	
Severe neutropenia (n=1)	1 (1.2)	-	
Chronic myeloid leukemia (n=1)	1 (1.2)	-	
Drug-induced lupus (n=1)	-	1 (2.5)	
Colon lymphoma (n=1)	-	1 (2.5)	
Colon adenocarcinoma (n=1)	-	1 (2.5)	

Table 3. Severe adverse events associated with the use of infliximab (IFX) and adalimumab (ADA) in a Northeast Brazilian cohort of 123 patients with inflammatory bowel disease (IBD).

Adverse event	Sex	Age (years)	IBD	TNF inhibitor	Time of use	Concomitant medication
Respiratory discomfort	F	25	UC	IFX	48m	AZA
Respiratory discomfort	F	37	CD	ADA	1m	AZA + corticóide
Sepsis †	F	31	CD	IFX	60m	AZA
Sepsis	F	46	CD	IFX	60m	AZA
Sepsis	F	54	CD	IFX	3 m	AZA
Sepsis†	F	22	CD	ADA	24m	None
Liver abscess	M	30	CD	ADA	60m	AZA + corticóide
Pleural tuberculosis	F	47	CD	IFX	4 m	AZA
Miliary tuberculosis	M	49	CD	IFX	1 m	AZA
Miliary tuberculosis†	F	26	CD	IFX	6m	AZA
Systemic candidiasis	F	24	CD	ADA	18 m	None
Colon adenocarcinoma	F	18	UC	IFX	36m	AZA
Colon lymphoma	M	18	CD	IFX	12m	AZA
Chronic myeloid leukemia	M	30	CD	ADA	12m	AZA
Drug-induced lupus	F	-	CD	IFX	17m	AZA

Female (F); Male (M); inflammatory bowel disease (IBD); Ulcerative colitis (UC); Crohn's disease (CD); Infliximab (IFX); Adalimumab (ADA); Azathioprine (AZA); Month (M); Deaths (†)

Mortality

Three deaths occurred (2.4%; 3/123), 2 in the IFX group and 1 in the ADA group. All were female. In the former group, one was diagnosed with CD, used IB agents + immunosuppressants for 5 years, and died of sepsis; the other was diagnosed with CD and died of miliary tuberculosis. In the latter group, a 22-year old patient used ADA for 2 years, with no concomitant medication, and died of sepsis, apparently of abdominal origin.

Infections

Infections were observed in 9 (IFX) and 4 (ADA) cases. Three of the 4 patients developing sepsis were treated with IFX, and 1 died. The fourth patient with sepsis was treated with ADA, and died. Two female patients with CD, ages 33 and 39, had urinary infection. They received IFX + immunosuppressants for 12 and 6 months, respectively, after which medication was stopped. Another female CD patient, aged 69 and treated with ADA for 2 years, presented urinary infection, and medication was discontinued. A 30-year old male CD patient developed liver abscess after taking ADA for 5 years. The abscess was successfully treated with antibiotics. Herpes zoster was diagnosed in a single CD patient treated with IFX. One patient in the ADA group developed systemic candidiasis requiring intensive care, with favorable outcome. A 47-year old female CD patient treated with IFX + immunosuppressants for 4 months developed pleural tuberculosis, making it necessary to discontinue the medication. Two patients treated with IFX had miliary tuberculosis. One died; the other experienced symptoms after only one month of IFX therapy, but improved with treatment for tuberculosis.

Acute reactions

Six of the 21 adverse events associated with IFX were acute reactions (5 skin rash/itching, 1 respiratory discomfort). The first five patients were aged 19-60 years, had been using IFX for 2-36 months and developed skin rash and itching after more than one administration, leading to the discontinuation of the treatment. Three of the 11 adverse events associated with ADA were acute reactions (2 skin rash/itching, 1 respiratory discomfort). A 24-year old female CD patient treated exclusively with ADA for 18 months experienced respiratory discomfort and bronchospasms after the administration, leading to the discontinuation of the treatment.

Psoriasis

Paradoxical psoriasis was observed in 4 patients (IFX n=3, ADA n=1). A 20-year old female CD patient treated with IFX for 2 years developed extensive psoriatic lesions. IFX was stopped and ustekinumab was initiated, with favorable outcome. Aged 20-75 years, the 4 patients presenting psoriasis all had a diagnosis of CD and had been treated with IB agents for 1 year (ADA) or 1-2 years (IFX) when medication was discontinued.

Neoplasia

An 18-year old female UC patient treated with IFX + immunosuppressants for 3 years was diagnosed with colon adenocarcinoma. The medication was stopped and the patient was submitted to colectomy and adjuvant chemotherapy. An 18-year old male CD patient treated with IFX + immunosuppressants for 1 year developed colon lymphoma. Finally, a 30-year old male CD patient treated with ADA + immunosuppressants for 1 year developed chronic myeloid leukemia, leading to the discontinuation of the treatment. The patient is currently monitored by the IBD service and the hematology service.

DISCUSSION

This is to our knowledge, one of the first studies that evaluated the side effects of IFX and ADA in the treatment of IBD in a Northeast Brazilian cohort. There is a study carried out in the southern region of the country and published in 2017, showed a high incidence of adverse events of IFX and ADA in the treatment of IBD.[7]

IFX is considered efficient at treating CD and UC, as shown by the ACCENT I/II and ACT I/II trials, respectively.[9] Likewise, the CLASSIC I/II and CHARM trials support the efficacy of ADA in this patient population.[10,11] TNF inhibitors are relatively well tolerated and have an adequate safety profile, but most of the data come from multicenter studies, in different countries. There are few studies on the safety profile of IBs in Latin American patients in the literature.[6,12]

In our cohort, 25% of the patients experienced adverse effects, regardless of the TNF inhibitor administered (IFX 21/83; ADA 10/40). In a retrospective study by Kamatand coworkers, 28.6% of 70 patients receiving biosimilar ADA at multiple Indian gastroenterology services experienced adverse events, 10% of which were severe, including 3 cases of tuberculosis.[8] Hanauerand colleagues discontinued IFX in 38 of 113 CD patients due to adverse events.[9] In the CLASSIC II trial, 43 (16%) of 276 CD patients stopped using ADA due to adverse events.[10] In the study carried out in southern Brazil, approximately two thirds of CD patients developed adverse events, 63.2% in IFX and 64.5% in patients with ADA (P = 0.879), with no difference between the two IBs, only one patient evolved with death (1/130).[7] These differences in the incidence of side effects highlight the importance of comparing cohorts from different regions.

The TREAT trial evaluated the long-term safety profile of IFX in CD patients based on a sample of 6,290 patients (IFX n=3,179; other therapies n=3,111). The authors observed 55 deaths (0.87%), of which 29 (0.53/100 patients-year) received IFX and 26 (0.43/100 patients-year) received other treatments (no significant difference).[13] Colombel and coworkers evaluated a cohort of 500 CD patients treated with IFX and determined the annual mortality rate to be 1.3%.[14] Another cohort of 152 patients diagnosed with CD, UC and indeterminate colitis were treated with IFX and followed on average for 142 weeks after the first dose. The drug was

associated with 64 adverse events in 49 individuals (32%), making it necessary to discontinue medication definitively in 14 cases (9.2%). The mortality rate was 2.6% (4/152).[15]

Mortality associated with IFX was higher in our study (2.44%) than in some other reports. This may be explained by socioeconomic factors (our study was conducted in a developing country with limited access to health care services) and/or by the concomitant use of immunosuppressants in many cases. The deaths in our cohort were due to sepsis and miliary tuberculosis, matching the results of the TREAT trial in which infection was the main cause of death.[13] In our study, 9 cases of infection were associated with IFX (10.85%), and 4 cases were associated with ADA (10%).

In the CHARM trial, 3.9-5.0% of the patients treated with ADA developed severe infections, including two cases of tuberculosis, but no deaths occurred.[11] In the 14th week of the TREAT trial, 22(4%) of 573 patients experienced severe infections. In the 56th week, the number had risen to 186 (32%).[13] A Swedish cohort of 217 patients treated with IFX registered 18 severe infections (8.29%) and 6 (2.8%) deaths, 2 of which were secondary to severe infections.[16]

One case of herpes zoster was observed in our cohort. Viral infections are known to be more frequent when IFX is combined with immunosuppressants. According to a single-center study from Belgium, in this scenario herpes virus is the main etiology. In that study, the risk of severe infections was significantly higher among patients combining IFX with corticoids.[6] Of the 13 patients developing infections in our study, 10 received a TNF inhibitor + immunosuppressants,1 received a TNF inhibitor + corticoids + immunosuppressants, and 2 received a TNF inhibitor only.

Acute infusional reactions were observed in 5 (6.0%) of 83 patients treated with IFX, matching the literature (3-17%).[14] In a study by Cheiftz and coworkers on a sample of 165 patients, most IFX-related infusional reactions were mild.[17] Acute infusional reactions were observed in 3 (7.5%) of 40 patients treated with ADA. The corresponding figure was 5% in a study by Ford and colleagues.[18]

Paradoxically, TNF inhibitors used to treat psoriasis can induce psoriasiform reactions through a poorly understood mechanism involving hypersensitivity and immune response.[19] According to one study, psoriasiform lesions may occur in 9-16% of patients treated with TNF inhibitors.[6] Up to 34% of patients with this side effect eventually discontinue the medication.[20] In our study, 3.6% (3/83) in the IFX group and 2.5% (1/40) in the ADA group developed psoriasiform lesions.

It is not clear how the human immune system protects against cancer, but cytotoxic lymphocytes and TNF binding to tumor cells are believed to play an important role in the initiation of apoptosis. Prolonged use of TNF inhibitors has therefore been hypothesized to increase the risk of neoplasia.[21] So far the evidence is inconsistent: in 10 clinical trials including 2,385 IFX users, the frequency of neoplasia was similar for IFX and placebo,[22] but the ACCENT trial reported 6 cases (1%) of neoplasia associated with IFX, including skin cancer, lymphoma, hypernephroma, breast cancer and bladder cancer.[9] Large longitudinal studies are required to clarify this issue, considering the extended latency of cancer.[15] In any case, it should be kept in mind that IBD patients are at greater risk of neoplasia than the general population. Early diagnosis (<15 years), extensive IBD, family history of colon cancer and association with primary sclerosing cholangitis are important risk factors for neoplasia, and patients with this profile are advised to have an annual colonoscopy.[23] In our study, 2 patients (2.4%) treated with IFX for over 12 months developed colon lymphoma and adenocarcinoma respectively. Moreover, 1 patient (2.5%) treated with ADA was diagnosed with chronic myeloid leukemia.

Few cases of neutropenia induced by TNF inhibitors in IBD patients have been reported. In one study involving 133 rheumatoid arthritis patients treated with TNF inhibitors, 14.3% experienced at least one episode of neutropenia.[24] Although the mechanism is not fully understood, TNF inhibitors seem to be able to induce autoimmune agranulocytosis due to the formation of auto-antibodies against granulocytes. In the above study, the median time from onset of treatment with TNF inhibitors to the emergence of neutropenia was 3 months, but in some cases it may be as little as 2 weeks.[25] In our study, a young CD patient developed neutropenia after three months of ADA therapy.

One of our female CD patients developed DIL associated with IFX. Despite the high incidence of antinuclear antibody formation, DIL is an infrequent finding in patients treated with TNF inhibitors.[26] In the literature, the incidence of DIL in CD patients treated with IFX is 0.19-1.6%,[27,28] while in a large study on 1,506 patients treated with ADA, 3 cases were observed.[29] The induction of auto-antibodies is believed to be a class effect associated with the deregulation of humoral autoimunity caused by TNF antagonism, but induction rates appear to differ substantially between different TNF inhibitors. Some authors have reported that exposure to a second TNF inhibitor increases the risk of DIL, but this claim requires further confirmation.[30]

Our study was limited by the small sample size, despite being conducted at a regional IBD referral service affiliated with the Unified Health Care System. Moreover, the cohort included patients with severe inflammatory disease and concomitant use of immunosuppressants, making it difficult to evaluate specific risk factors for mortality and control for confounders. On the other hand, the study population was homogeneous, treatment compliance was adequate, and no subjects were lost to follow-up.

CONCLUSION

Matching the literature, the present retrospective cohort study found long-term use of TNF inhibitors in the treatment of IBD to be reasonably safe, although careful screening and monitoring are necessary to identify and follow patients with increased risk of side effects, some of which may be severe.

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