Original Article

Adalimumab in the induction of Crohn's disease remission: results of a Brazilian multicenter case series

PAULO GUSTAVO KOTZE[1], ANDREA VIEIRA[2], CARLOS WALTER SOBRADO JUNIOR[3], JULIANA BARRETO SALEM[4], LORETE MARIA DA SILVA KOTZE[5]

[1]Coordinator of the Proctology Service at Hospital Universitário Cajuru (SeCoHUC), Pontifícia Universidade Católica do Paraná (PUC-PR) – Curitiba (PR), Brazil. [2]Head of the Gastroenterology Clinic at Irmandade de Misericórdia Santa Casa de São Paulo – São Paulo (SP), Brazil. [3]Doctor at the Coloproctology Service of Hospital da Polícia Militar do Estado de São Paulo – São Paulo (SP), Brazil. [4]Doctor at the Surgery Service of Hospital Municipal de Urgência of Guarulhos – Guarulhos (SP), Brazil. [5]Head Professor of the Gastroenterology Service at Hospital Universitário Cajuru, PUC-PR – Curitiba (PR), Brazil.

KOTZE PG, VIEIRA A, JUNIOR CWS, SALEM JB, KOTZE LMDS. Adalimumab in the induction of Crohn's disease remission: results of a Brazilian multicenter case series. **Rev bras Coloproct,** 2011;31(3): 233-240.

ABSTRACT: Introduction: Adalimumab (ADA) is a subcutaneous fully-human anti-TNF antibody which has a significant role in the management of Crohn's disease (CD). Its efficacy has been demonstrated in several clinical trials. The main objective of this study was to evaluate the role of ADA in the induction of clinical remission in a Brazilian series of CD cases. Method: A retrospective analysis of CD patients treated with ADA was performed in three Brazilian inflammatory bowel diseases (IBD) reference centers. The following characteristics were analyzed: gender, age, indication to ADA treatment, type of response, previous exposure to infliximab (IFX), concomitant use of immunomodulators and adverse events, among others. Results: 54 patients (29 females) were included in this series, with mean age of 36.72 years (ranging from 15 to 62 years). After induction regimen, 26 patients (48.14%) were in clinical remission, 26 (48.14%) had partial response, and 2 (3.72%) were primary non-responders. After a mean follow-up of 9.83 (2 to 28) months, 17 patients (31.48%) presented adverse events. The most common event was pain on the injection site (7 patients – 12.96%). Conclusions: ADA was effective to induce CD remission in this Brazilian case series. The remission and response rates were similar to the literature, as well as the safety profile of this drug.

Keywords: Crohn's disease; tumor necrosis factor-alpha; remission induction; antibodies, monoclonal.

INTRODUCTION

Crohn's disease (CD) has always been considered as challenging for patients and health professionals, because it is incurable and difficult to treat. In the past 60 years, different drugs have been used in the treatment with limited efficacy and considerable adverse effects. Starting with derivatives of the 5-aminosalicylic acid (5-ASA) and steroids, then moving on to antibiotics and immunomodulators, it was not possible to change the natural history of CD; as a consequence, it was common to observe its evolution to more severe forms[1].

Study carried out at the Proctology and Gastroenterology services of Hospital Universitário Cajuru, Pontifícia Universidade Católica do Paraná, Curitiba (PR), and at Hospital da Polícia Militar do Estado de São Paulo and the Gastroenterology Service of Irmandade de Misericórdia da Santa Casa de São Paulo, São Paulo (SP), Brazil.
Financing source: none.
Conflict of interest: nothing to declare.

Submitted on: 31/01/2011
Approved on: 02/03/2011

The tumor necrosis factor (TNF) therapy represents the ultimate advance regarding the treatment of CD, and is currently used in daily clinical practice[2]. The first biological drug commercially available for this purpose was Infliximab (IFX), an intravenous chimeric antibody. Randomized clinical trials on IFX published in the early 2000s represented a turning point to treat these patients, since they resulted in significant clinical remission and response rates in patients with moderate and severe CD[3,4].

In order to reduce immunological responses induced by chimeric fractions of IFX, there was the attempt to develop fully human monoclonal antibodies[5]. Recently, the use of Adalimumab (ADA) was permitted by regulatory bodies in many countries for the treatment of CD. In Brazil, this drug has been used for this purpose since 2007, and the experience with this medication has been increasing. ADA can also be indicated for the treatment of adult patients with moderate or severe active CD, who no longer respond or are intolerant to IFX[6]. However, better results have been demonstrated in patients who have never used anti-TNF agents[7].

It is a fully human recombinant IgG1 monoclonal antibody (with 100% of human peptide sequences), with subcutaneous self-administration[5]. ADA inhibits the tumor necrosis factor-alpha (TNF-α), leading to the apoptosis of inflammatory cells and the consequent reduction of tissue inflammation. ADA's clinical efficiency and safety have been demonstrated in several phase III clinical trials, randomized and double-blind. Among these, the studies CLASSIC I, CLASSIC II, CHARM and GAIN stand out, and include a total of 1,754 patients[5-8].

Afterwards, many real life studies were published in literature, showing case series of many countries, such as Australia, Spain, among others[9,10]. There is no data in the literature regarding the efficacy of ADA in Brazilian patients as to CD management. Thus, it is necessary to conduct a more detailed assessment of Brazilian patients with CD, and this fact encouraged the authors to perform this study.

The main objective of this paper was to assess the clinical efficacy of ADA to induce CD clinical remission in a series of Brazilian patients coming from three reference centers of inflammatory bowel diseases (IBD). The secondary objectives included the analysis of demographic data, drug's safety (presence of adverse effects) and reasons to discontinue the treatment, among other variables.

METHOD

This study was previously approved by the Research Ethics Committee of *Pontifícia Universidade Católica do Paraná* (CEP – PUC-PR), n. 5087/2009. It is an open, retrospective and analytical study concerning a case series. The studied sample consisted of patients with CD being treated with subcutaneous ADA. They came from three reference centers of inflammatory bowel diseases (IBD), one from the South and two from the Southeast region in Brazil. Data were collected from the patients' medical records, and a specific protocol that had been previously established was filled. The analyzed variables were:

- Age;
- Gender;
- Weight;
- Corticoid dependency;
- How the disease is presented (luminal, stenosing or penetrating);
- Presence of anal and abdominal fistulae at the treatment;
- Prior anal and abdominal surgeries;
- Treatment strategy (step-up or top-down);
- Use of immunosuppressors;
- Type of response after the induction therapy (total, partial or absent);
- Follow-up time to maintain the treatment;
- Presence of adverse effects;
- Reasons to discontinue the treatment.

The study included all the patients who had been submitted to the subcutaneous ADA treatment (Humira®, Abbott Laboratórios do Brasil Ltda.) to handle CD in a period of two years (from October 2007 to September 2009). The patients came from the three aforementioned reference centers (one from Curitiba – PR, and two from the city of São Paulo – SP). The main inclusion criterion for this study was the performance of the doses of remission induction, which corresponds to 160 mg on week 0 and 80 mg on week 2. All patients received this dose (four subcutaneous syringes of 40 mg each on week 0, and two subcutaneous syringes of 40 mg on week 2). The patients could be on immunosuppressors or not, and could also have previously used another anti-TNF agent or not (IFX).

Patients with a different induction dose were excluded from the study (80/40 mg or absent).

All data were collected by the researchers, being compiled in tables for further analyses.

The main idea to be analyzed as to efficacy was the way patients responded to the drug, after remission induction in the first two weeks; the analysis took place on week 4. Total response was defined as clinical remission (absence of symptoms after the period of induction). Partial response was subjectively defined as the improvement of symptoms, without their complete absence (residual symptoms, however, less intense than before the treatment). Absence of response was defined as the lack of clinical improvement due to the treatment (primary non-responders). This classification was in accordance with the one used in a similar methodology study, by Palacios et al., published in 2008[9]. No quantitative methods were used to analyze the clinical response to the treatment, such as the Crohn's disease activity index (CDAI) or the Harvey-Bradshaw index.

All patients were submitted to the maintenance treatment, with 40 mg of ADA every two weeks, for a variable period of time. In order to analyze the adverse effects and the reasons to discontinue the treatment, not only the period of remission induction was calculated, but also the doses subsequent to the maintenance of the treatment. The information was compiled in a specific spreadsheet for the final data analysis.

To evaluate the type of response after the induction, no specific statistical analysis was used, only frequency tables. To analyze the type of response in relation to the use of immunosuppressors and prior use of IFX, the Chi-squared test was performed to compare the three groups. Fischer's exact test was only used to analyze the relation between the total and partial responses as to the prior use of IFX. Significance level for these analyses was 95% ($p<0.05$).

RESULTS

Fifty-four patients with CD and history of treatment with ADA were included in this study. Mean age of the patients was 36.72 (15-62) years, and mean weight was 58.25 (36-102) kg. In relation to gender, out of the 54 patients, 25 were males and 29 were females. As to the disease presentation, 19 patients had the luminal disease, 7 had the stenosing disease and 28 presented the penetrating form (fistulizing). Out of the analyzed cases, 30 depended on corticoids for the treatment. These and other general characteristics of the patients, such as the presence of fistula, abdominal surgery, prior use of immunomodulators or IFX are demonstrated in Table 1.

Out of the sample of 54 patients, 26 (48.14%) presented complete clinical remission (total response) on week 4, and 26 (48.14%) presented partial response; only 2 (3.72%) were primary non-responders. These findings are demonstrated in Figure 1.

The relation between the type of response and the use of immunomodulators (in all cases, azathioprine 2 mg/kg) was also analyzed. Out of the 26 patients with total response after induction, only one used monotherapy with ADA. From the 26 patients who partially responded, five were not on immunomodulators and used monotherapy. The two primary non-responders used azathioprine. These findings are demonstrated in Figure 2. None of the patients in this

Table 1. *General characteristics of the patients (n=54).*

Mean age	**36.72 years (15-62 years)**	
Gender	Male	25 (46.3%)
	Female	29 (53.7%)
Mean weight	**58.25 kg (36-102 kg)**	
Corticoid dependency	Yes	30 (55.5%)
	No	24 (44.5%)
How the CN disease is presented	Luminal	19 (35.2%)
	Stenosing	7 (13.0%)
	Penetrating	28 (51.8%)
Anal fistulae	Yes	27 (50.0%)
	No	27 (50.0%)
Abdmonial fistulae	Yes	6 (11.1%)
	No	48 (88.9%)
Prior anal surgeries	Yes	18 (33.3%)
	No	36 (66.7%)
Prior abdominal surgeries	Yes	26 (48.1%)
	No	28 (51.9%)
Prior use of immunosuppressors	Yes	48 (88.9%)
	No	6 (11.1%)
Previous use of IFX	Yes	30 (55.5%)
	No	24 (44.5%)
Treatment strategy	*Step-up*	48 (88.9%)
	Top-down	6 (11.1%)

series used methotrexate or another immunomodulator. There were no statistical differences between the groups as to the presence of immunomodulator in the type of response, according to the Chi-squared test.

Another interesting fact in this sample was the type of response obtained after the remission induction in relation to the prior use of IFX. Out of the 25 patients who presented total response (remission), 16 had previously used IFX, as well as 14 out of the 26 patients with partial response to ADA. Both cases of primary non-responders in this study had not used IFX. These findings are demonstrated in Figure 3. There were no statistical differences among the three groups according to the Chi-squared test and Fischer's exact test (used only to compare remission and partial response).

In order to analyze secondary objectives, the maintenance of biological treatment with ADA in all patients was registered. Mean follow-up time was 9.83 months, ranging from 2 to 28 months. Out of the 54 patients analyzed in this study, nine had to discontinue the treatment with ADA. From these, six could not access the drug due to bureaucracy motives (difficulties with the health insurance or the public system). Out of the three patients who discontinued the treatment due to clinical reasons, one presented with diffuse urticariform eczema (Figure 4); the other presented bronchopneumonia, and the last one had hesper zoster. After the treatment of these adverse events, ADA injections were reestablished at the average maintenance dose (40 mg every 2 weeks), and the follow-up of these patients was not included in the rest of the analyses.

From the whole sample, 17 (31,48%) patients had adverse effects. The total number of events was 21, which means that four patients presented two adverse events. The most common effect was pain in the site of subcutaneous injection in 12.96% of the patients (seven cases). Infection by herpes simplex occurred in three patients (5.55%). The other adverse effects are listed in Table 2.

DISCUSSION

The efficacy and the safety bprofile of ADA to manage CD are currently well established, after the performance of several randomized studies[5-8]. The requirements for a study with such great characteristics

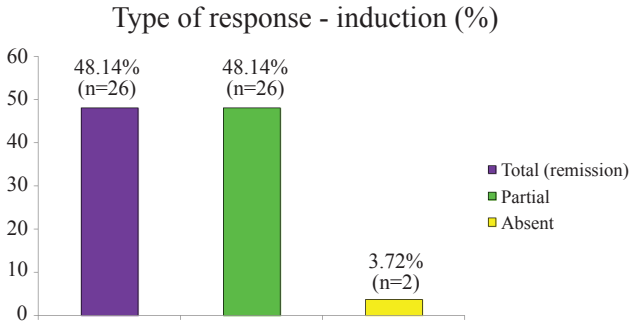


Figure 1. *Total, partial or absent response rates, analyzed four weeks after remission induction in all included patients (n=54). The clinical remission was defined as the absence of symptoms, the partial response, as clinical improvement at the presence of residual symptoms, and absent in patients with no improvement.*

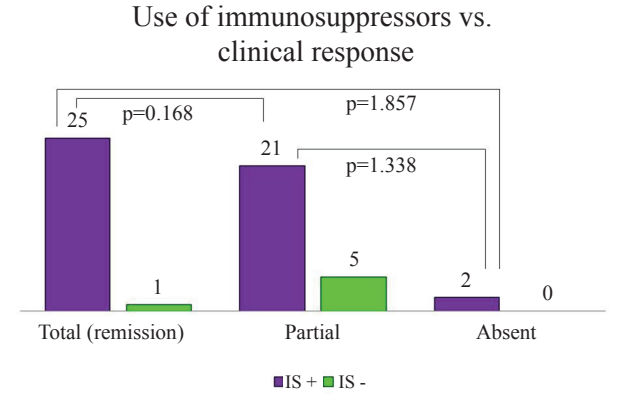
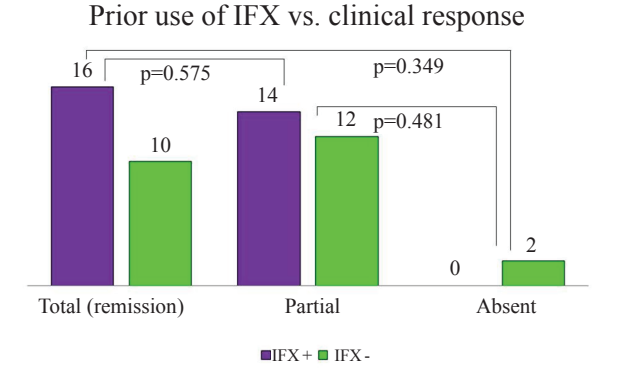


Figure 2. *Type of response in relation to the use of immunosuppressors (azathioprine). Absence of statistical differences between the three groups (Chi-squared test).*



IFX: Infliximab

Figure 3. *Type of response in relation to the prior use of IFX. Absence of statistical differences between the three groups according to the Chi-squared test and Fischer's exact test (used only to compare partial response and remission).*

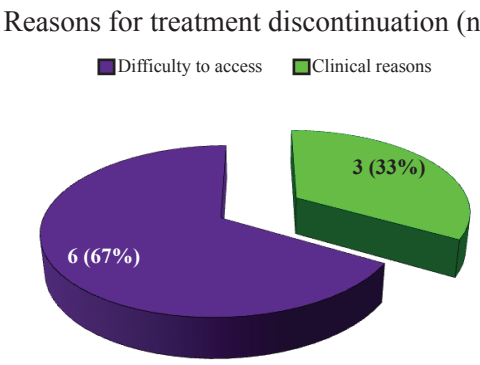


Figure 4. *Reasons that led nine patients to discontinue treatment with subcutaneous adalimumab.*

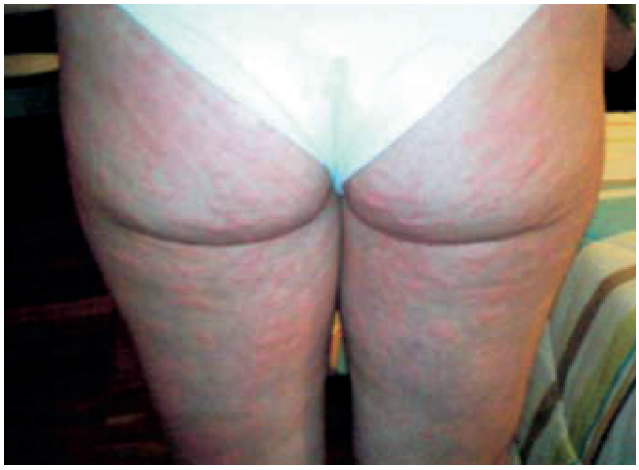


Figure 5. *Diffuse urticariform eczema after two doses of adalimumab. Adverse effect that led to the temporary discontinuation of the drug.*

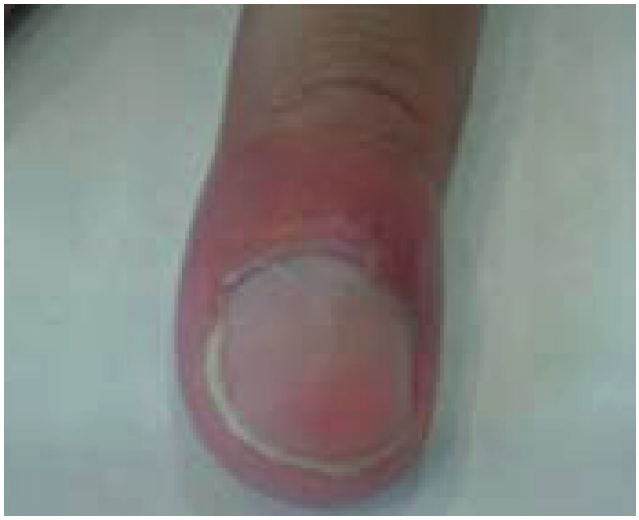


Figure 6. *Ungual inflammation in a patient on adalimubab. Simple adverse effect, which did not require the interruption of the treatment.*

Table 2. *Adverse effects ot the treatment with adalimumab in the case series (n=17 out of the 54 patients). Only four patients presented two adverse effects, accounting for 21 events. Mean follow-up of 9.83 months.*

Adverse effect	n (%)
Pain at the injection site	7 (12.96)
Herpes simplex	3 (5.55)
Urinary tract infection	2 (3.7)
Ungual inflammation	2 (3.7)
Headache	2 (3.7)
Arthralgia	1 (1.85)
Eczema	1 (1.85)
Bronchopneumonia	1 (1.85)
Amigdalitis	1 (1.85)
Herpes Zoster	1 (1.85)

are many, and there is a good chance for a strict analysis of primary and secondary outcomes of these studies. This means that, in outpatient clinics and offices, it is possible to succeed with the patients regarding the management of biological therapy for CD.

After the publication of these renowned papers, literature started to present retrospective case series of patients with CD treated with ADA. These series came from different countries in the world, and showed clinical remission rates after the remission induction dose (160/80 mg), which was different from that found in controlled studies, especially in CLASSIC I[5]. The total response index (clinical remission) found in this study, of 48.13% of the cases, is higher than the 25% found in CLASSIC I, a study exclusively designed for the clinical remission outcome after induction. One of the factors that may explain these high levels was that 51.9% of the patients had the penetrating disease with active inflammation, and, in this case, response tends to be better. By adding the patients in remission and those with partial response, the result was impressive: 96.2% of improvement with ADA in the patients of this series. This number is probably due to the limitations of a retrospective methodology and to the non-definition of strict disease activity rates (such as CDAI), with a more subjective analysis.

Palacios et al., a Spanish team, found 25% of remission and 56.3% of partial response after the

same induction dose, for the luminal CD[9], using the Harvey-Bradshaw index. For the fistulizing disease, observed in six patients, one case presented remission (16.7%), four patients had partial response (66.7%). This paper was conducted with a methodology similar to the one used in this study, and had a small sample of 22 patients.

Trinder et al. published a study in 2009 representing a case series of Australian patients with CD, and found 54.5% of clinical remission and 27.3% of partial response[10]. It is important to emphasize that, in this study, the analysis as to the type of response was conducted in the eighth week, which may have increased these numbers, since cohort studies with long-term follow-up of patients demonstrated that remission rates and response to biological therapy can be optimized until week 20, in cases in which the treatment maintenance occurs[11].

Swaminath et al. analyzed the results of ADA in 48 patients. They reported remission in only 2% of the cases, with 43.8% of clinical improvement subjectively determined by the patient's assistant[12]. Findings from the main studies of literature regarding remission and response to CD with ADA are demonstrated in Table 3.

Two reasons may explain the higher success rates regarding therapy in retrospective studies. First, patients are less selected than the rigid inclusion criteria of randomized trials, as aforementioned. Second, cohort patients throughout the world usually present with active inflammation, and it is known that, in these patients, treatment tends to be more efficient, especially for those with high levels of C-reactive protein (CRP)[13].

Table 3. *Main findings as to remission and clinical response to adalimumab found in literature, compared to this study.*

Author, year	Remission (%)	Response (%)
Hanauer et al., 2006 (CLASSIC I)[5]	36.0	59.0
Palacios, 2008[9]	22.7	59.1
Trinder et al., 2009[10]	54.5	81.8
Kotze et al., 2011 (present study)	48.13	48.13

In relation to the number of primary non-responders, the findings in this study (3.72%) are lower than the ones found in literature. In a study with a mean follow-up of 55 months with IFX, in the cohort of Leuven, Belgium, Schnitzler et al. identified that 10.9% of the 614 IFX users were primary non-responders[14]. In the aforementioned Australian study, 18.2% of the ADA users did not present any response[10]. A very similar number was found in the Spanish study, in which 4 out of the 22 patients did not respond to ADA induction, corresponding to 18.1% of the cases[9]. The exact proportion of non-responders to induction with ADA in literature is unknown, since data from randomized studies are not clear. However, the low rates of patients with no response in this retrospective series can be explained by the subjectivity in the analysis of the used answer.

Corticoid dependency was found in 30 out of the 54 cases in this study (55.5%). Besides, the strategy ascending from the treatment (step-up) was used in 48 patients (88.9% of the cases). With these numbers, it is possible to observe that, in relation to these patients, who represented the early experience of the three reference centers of this case series with ADA, there was the trend to use biological treatment in a significantly conservative way. More recently, criteria of CD worse prognosis have been defined in literature, which will certainly increase rates of more aggressive therapy in the future. In the reference centers mentioned in this study, there probably will be more cases of descending strategy (top-down).

The use of immunosuppressors with the biological therapy may influence the efficacy of the antibodies in CD. However, literature shows controversies in relation to this topic. The study called SONIC, published in 2010, was exclusive designed with this purpose[15]. It was a randomized study with patients who had CD, and had never used anti-TNF agents or immunosuppressors. The results in that study demonstrated that the combined use of IFX and azathioprine had better clinical remission rates without corticoids and mucosal healing than the group with IFX as monotherapy.

There are no studies with the same objective regarding ADA in literature. A subanalysis of the

study CHARM did not show any differences as to the efficacy of ADA in patients using azathioprine or not[7]. However, this study focused on therapy maintenance and lasted a year. In the present study, it was possible to analyze the role of azathioprine together with ADA, in relation to monotherapy with the biological agent, because almost all patients (48 out of the 54 in the sample) were treated with the combined therapy. The number of patients on monotherapy was small, which was partially negative for the analysis. Despite that, the statistical analysis showed no significance. However, the study was not designed for this purpose.

Another controversy as to biological therapy for CD is the previous use of another TNF-agent in the treatment. Since IFX was approved seven years before ADA in Brazil, one of the reasons to use ADA is the lack of or the intolerance to the previously used IFX. Even though the authors in this study are experienced in relation to the use of IFX when ADA fails to work in a few cases, there is no randomized trial in literature with this purpose.

Clearly, the concept that exists in literature is that patients who had never used IFX respond better to ADA subcutaneous injections than those who have previously tried another biological agent. This can be demonstrated in randomized trials and in a recent meta-analysis published by a Canadian group[16]. It is known that around 2/3 of the patients who had never used IFX respond better to ADA. However, for those patients who have been previously exposed, those rates are reduced. The study GAIN was exclusively designed with this purpose, and demonstrated that 21% of the patients were in complete clinical remission after induction, and that 50% of them responded to treatment[6]. On the other hand, the sample of this important study about ADA includes patients who have had adverse reactions to IFX and those with loss of response to the drug. This difference as to ADA may have influenced the results, since it is more efficient for intolerance due to adverse events than for loss of response.

In this case series, there was no significantly statistical difference between patients who used IFX or not in remission and partial response levels, which is not in accordance with literature. Absolute numbers even show the opposite pattern. There is no justification for these results, however, it is believed that with more patients, there could be a better conclusion as to the effect of the previous use of IFX in patients treated with ADA.

In relation to the adverse effects observed in this series, the findings are in accordance with literature. In a review of all controlled trials about ADA in CD, which included 3,160 patients, Colombel et al.[17] demonstrated adverse events in up to 60% of the cases. These events ranged from simple situations, like hematomas and pain at the site of injection, to serious infections. The findings in this study showed adverse effects in 31.48% of the cases, which is a lower percentage in comparison to the information in randomized studies.

The authors of this review regarding the safety of ADA found severe adverse effects in 34.4 patients/year, which led to the discontinuation of treatment in 16.3 patients/year. In this study, 3 out of the 54 patients (5.55% of the cases) needed to discontinue treatment due to clinical reasons. The low number may be explained by the short follow-up time. Infections were the most frequent and severe events, in accordance with literature. The estimated mortality with ADA was of 4 among 3,160 patients, which is lower than CD mortality[17]. The malignancy incidence in literature was present in 44 out of the 3,160 analyzed patients, with only two cases of lymphoma. There were no deaths or malignancy in the present series.

CONCLUSIONS

The use of ADA in this case series showed high rates of remission and clinical response, and also a low number of primary non-responders. These results can be compared with those of retrospective studies found in literature. There was a significant number of patients who needed to discontinue the treatment, especially for bureaucratic motives (difficulty to access the medication) rather than clinical reasons. Rates and types of adverse events were similar to those of literature.

With this first case series about ADA in Brazilian patients who have CD, the conclusion is that the drug is efficient and safe, similar to the findings from other series in different countries of the world.

RESUMO: Introdução: O adalimumabe (ADA) é um anticorpo anti-fator de necrose tumoral alfa totalmente humano, de uso subcutâneo, com eficácia e perfil de segurança bem determinados na doença de Crohn (DC). O objetivo principal deste estudo foi determinar o papel do ADA na indução da remissão na DC, em uma série brasileira de casos. Método: Estudo retrospectivo, realizado em três centros de referência em doenças inflamatórias intestinais, com usuários do ADA para tratamento da DC. As variáveis analisadas foram: idade, sexo, indicação do tratamento, forma de apresentação da doença, tipo de resposta (total, parcial ou ausente), exposição prévia ao Infliximabe (IFX), entre outras. Resultados: 54 pacientes foram analisados (29 mulheres), com média de idade de 36,72 (15 a 62) anos. Após a dose de indução da remissão, 26 pacientes (48,14%) apresentaram resposta total (remissão clínica), 26 (48,14%) tiveram reposta parcial e 2 (3,72%) foram não-respondedores primários. Após seguimento médio de 9,83 (entre 2 e 28) meses, 17 pacientes (31,48%) apresentaram efeitos adversos (o mais comum foi dor no local da injeção em 7 pacientes – 12,96%). Conclusões: O ADA se mostrou efetivo na indução da remissão na DC em pacientes brasileiros, com taxas de remissão clínica e resposta compatíveis com as da literatura.

Palavras-chave: doença de Crohn; fator de necrose tumoral alfa; indução de remissão; anticorpos monoclonais.

REFERÊNCIAS

1. Vermeire S, Van Assche G, Rutgeerts P. Review article: altering the natural history of Crohn's disease – evidence for and against current therapies. Aliment Pharmacol Ther 2006;25:3-12.
2. Rutgeerts P, Van Assche G, Vermeire S. Review article: infliximab therapy for inflammatory bowel disease – seven years on. Aliment Pharmacol Ther 2006;23:451-63.
3. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-9.
4. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's Disease. N Engl J Med 2004;350:876-85.
5. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas N, Macintosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130(2):323-33.
6. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, et al. Adalimumab induction therapy for Crohn's disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007;146:829-38.
7. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132(10):52-65.
8. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, Macintosh D, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56:1232-9.
9. Palacios NL, Mendoza JL, Taxonera C, Lana R, Ferrer MF, Díaz-Rubio M. Adalimumab induction and maintenance therapy for Crohn's disease. An open label study. Rev Esp Enferm Dig 2008;100(11):676-81.
10. Trinder MW, Lawrance IC. Efficacy of adalimumab for the management of inflammatory bowel disease in the clinical setting. J Gastroenterol Hepatol 2009;24:1252-7.
11. Reinisch W, Louis E, Lofberg R, Kron M, Camez A, Robinson A, et al. Influence of disease duration on adalimumab efficacy in Crohn's disease: Subanalysis of the CARE Trial. Presented at ECCO congress, Hamburg, Germany; 2009.
12. Swaminath A, Ullman T, Rosen M, Mayer L, Lichtiger S, Abreu MT. Early clinical experience with adalimumab in treatment of inflammatory bowel disease with infliximab-treated and naïve patients. Aliment Pharmacol Ther 2009;29(3):273-8.
13. Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OØ, Hanauer SB, McColm J, et al. PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 2007;357(3):239-50.
14. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58(4):492-500.
15. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362(15):1383-95.
16. Ma C, Panaccione R, Heitman SJ, Devlin SM, Ghosh S, Kaplan GG. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. Aliment Pharmacol Ther 2009;30(10):977-86.
17. Colombel JF, Sandborn WJ, Panaccione R, Robinson AM, Lau W, Li J, et al. Adalimumab safety in global clinical trials of patients with Crohn's disease. Inflamm Bowel Dis 2009;15(9):1308-19.

Correspondence to:
Paulo Gustavo Kotze
Rua Mauá, 682, Juvevê
CEP: 80030-200 – Curitiba (PR), Brazil
E-mail: pgkotze@hotmail.com