



Journal of Coloproctology

www.jcol.org.br



Original article

Analysis of the factors related to anti-TNF alpha response in the treatment of Crohn's Disease

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ARTICLE INFO

Article history:

Received 13 October 2013

Accepted 23 December 2013

Keywords:

Crohn's disease

Infliximab

Adalimumab

Treatment

Age

Gender

ABSTRACT

Crohn's disease (CD) presents a great challenge regarding treatment, considering that the best drugs available have very limited effectiveness.

Objective: To analyze the characteristics between groups of patients with Crohn's disease who had response versus had not/lost response to treatment with anti-TNF.

Method: Retrospective study of patients with CD treated with IFX or ADA.

Results: We studied 72 patients with mean age of 35 years; 45 of them were treated with infliximab and 27 with adalimumab; 90% of women were respondents, compared to 10% who were not respondents/lost response, and 60% of men were respondents versus 40% who were not respondents/lost response; there was no difference between IFX and ADA with respect to response; 48 patients were < 40 and 24 > 40 years old. Of those who had < 40 years, 37 were respondents, compared to 11 who were not respondents/lost response. Of those with > 40 years, 16 were respondents versus 8 who were not respondents/lost response; patients under 2 years of diagnosis had a better response than those with two to five years of symptoms, and these latter exhibited a better response than those with more than five years of diagnosis.

Conclusion: The observed characteristics of response to treatment of CD with anti-TNF were: association to azathioprine, female gender, age < 40 years and less than two years of diagnosis.

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<http://dx.doi.org/10.1016/j.jcol.2013.12.006>

Análise dos fatores relacionados à resposta e à ausência/perda de resposta ao anticorpo antifator de necrose tumoral-alfa no tratamento da doença de Crohn

R E S U M O

Palavras-chave:
Doença de Crohn
Infliximabe
Adalimumabe
Tratamento
Idade
Gênero

A doença de Crohn (DC) apresenta um grande desafio quanto ao seu tratamento, considerando-se que os melhores medicamentos disponíveis têm eficácia bastante limitada. *Objetivo:* Analisar as características entre os grupos de pacientes com DC que responderam e os que não responderam ou perderam a resposta ao tratamento com anti-TNF. *Método:* Estudo retrospectivo de pacientes com DC que fizeram uso de IFX ou ADA. *Resultados:* Foram estudados 72 pacientes com média de idade de 35 anos; 45 foram tratados com adalimumabe e 27 com infliximabe; 90% das mulheres tiveram resposta, contra 10 que não tiveram/perderam resposta; dos homens, 60% tiveram resposta contra 40% que não tiveram/perderam resposta; não houve diferença entre IFX e ADA quanto à resposta; 48 tinham menos de 40 anos e 24 mais de 40 anos. Dos com < 40 anos, 37 tiveram resposta, contra 11 que não tiveram/perderam resposta. Daqueles com > 40 anos, 16 tiveram resposta contra 8 que não tiveram/perderam resposta; pacientes com menos de 2 anos de diagnóstico tiveram melhor resposta do que aqueles com dois a cinco anos de sintomas; e estes tiveram melhor resposta que aqueles com mais de cinco anos de diagnóstico.

Conclusão: As características observadas de melhor resposta ao tratamento da DC com anti-TNF foram associação com azatioprina, gênero feminino, idade menor de 40 anos e menos de dois anos de diagnóstico.

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Introduction

Crohn's disease (CD) has been a major challenge for physicians treating inflammatory bowel diseases. Since its description in 1932, by Burrill Crohn et al.,¹ a lot of information was obtained in relation to its pathophysiology and therapeutics, with more significant advances in the last two decades with regard to treatment. However, one should take into account that there is still much to be discovered, since our best combination therapy benefits persistently no more than 40% of patients.²

If on one hand we must seek – and we are seeking – new drugs that improve the therapeutic efficacy, on the other hand we should strive to achieve more efficient methods to employ our present knowledge, but with strategies to achieve better results. In this respect, we must emphasize the great contribution of Colombel et al.,³ who were more successful with the combination of infliximab and azathioprine versus monotherapy with each of these drugs.

The evaluation of the presence of anti-biological agent antibodies and the dosage of circulating levels of these drugs have been shown to be of great value, but such procedures are not yet widespread in most Brazilian cities, due to their cost.

The evaluation of results obtained from the use of anti-TNF therapy may be helpful, if it is shown that in certain indications for its use in DC patients a better response to one or another biological agent is obtained. Currently, the indications for these drugs in DC are the same.⁴

Thus, the objective of this trial was to analyze the characteristics between groups of patients who had responded

versus did not respond or lost response to a treatment with anti-TNF.

Method

A retrospective study of medical records of patients from the Inflammatory Bowel Diseases Outpatient Service, Hospital Universitário Maria Aparecida Pedrossian, Universidade Federal de Mato Grosso do Sul, Hospital Regional de Mato Grosso do Sul, and at the private practice of the author.

Patients with Crohn's disease who were referred and made use of anti-TNF agents were included. All patients included were previously investigated for presence of TB and hepatitis B.

The study period was from June 2000 to July 2013. The anti-TNF agents were used at recommended doses and intervals: infliximab (IFX) 5 mg/kg at weeks 0, 2 and 6, with maintenance at every 8 weeks; and adalimumab (ADA) 160 mg on week 0, 80 mg on week 2 and 40 mg at every 2 weeks.

Patients with perianal fistulas were treated by curettage and placement of a seton, with successive changes, if necessary, until it was possible to remove the drain. On average, the biological therapy in these patients was introduced one week after surgery.

We considered as a clinical response to anti-TNFa the reduction of Crohn's disease activity index of (DCAI) ≥ 100 points⁵ and, in cases of perianal fistulas, absence of pain and secretion for more than six months.

The results were statistically analyzed by Student's *t* test and chi-square test, and $p < 0.05$ was considered statistically significant.

Results

72 patients, 40 (55%) male and 32 (45%) female, were studied. The age ranged from 14 to 59 years old, with a mean of 35 years. The main indications for the use of anti-TNF agents are listed in Table 1.

The choice of anti-TNF agent was based on preference of patients and availability of the agent, similarly to information from the literature on the subject.^{6,7} Of the 72 patients, 45 (62.5%) were treated with adalimumab and 27 (37.5%) with infliximab (Fig. 1).

In our population of 72 patients, 53 remained with the same agent originally prescribed, considering that they obtained clinical response. On average, the time of drug use was 18 months, ranging from one to 60 months.

Of these 53, eight patients were not treated with immunosuppression in combination with anti-TNF, considering that many of these individuals had their treatment started before there was medical evidence favouring this therapeutic approach.³ The remaining 45 patients made use of anti-TNF in combination with azathioprine (AZA) (2-3 mg/kg/day),⁸ but five of them discontinued the use of this agent, due to intolerance. Therefore, 40 (75%) patients remained in the combined treatment: 23 on ADA

+ AZA and 17 on IFX + ADA. Respecting to the 19 patients who did not respond/lost response, 11 (58%) had an immunosuppressive associated (Fig. 2).

Women showed better response to anti-TNF therapy than men, since that 29 women (90% of women) kept using it versus 24 men (60% of men) (Fig. 3).

When the response in relation to anti-TNF agent was analyzed, there was no statistically significant difference between groups. Of the 45 patients treated with ADA, 33 had a response (73%) and 12 did not respond/lost response (27%). Of those who received IFX, 20 had a response (74%) and seven did not respond/lost response (26%) (Fig. 4); $p = 0.5$.

Forty-eight patients were < 40 and 24 > 40 years old. Of those who were <40 years, 37 had a response, compared with 11 who did not respond/lost response. Of those with > 40 years, 16 had a response, against eight who did not respond/lost response (Fig. 5); $p = 0.000358$.

Table 1 – Indications for the use of anti-TNF agents in the group studied.

Indications	Number of patients
Age <40 years	45
Perianal fistula	30
Extensive disease in small intestine	26
Intractability	24
Stenosing disease	9
Extra-intestinal disease	4
Deep ulcers at colonoscopy	4
Corticodependence	3
Rectovaginal fistula	2
Enterointestinal fistula	2
Growth deficit	2
Toxic megacolon	1

Some patients had more than one indication.

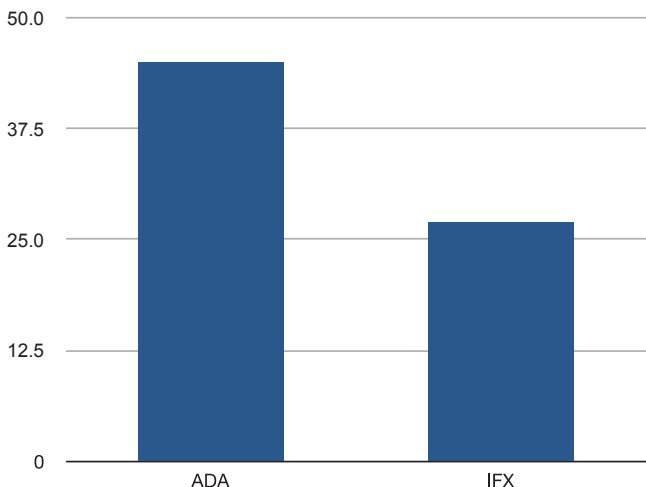


Fig. 1 – Anti-TNF agents used according to preference of patients. ADA, adalimumab; IFX, infliximab.

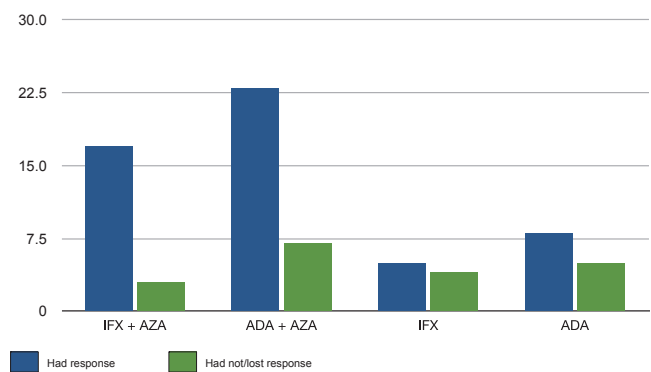


Fig. 2 – Comparison between groups of patients who had a clinical response to anti-TNF and who lost/had no answer for the use of an immunosuppressant (azathioprine) associated. In the group which had response, comparison between IFX + AZA and ADA + AZA versus IFX and ADA, $p = 0.0000193$, while among those who lost/had no answer, comparison between IFX + AZA and ADA + AZA versus IFX + AZA, $p = 0.30550$. IFX, infliximab; AZA, azathioprine; ADA, adalimumab.

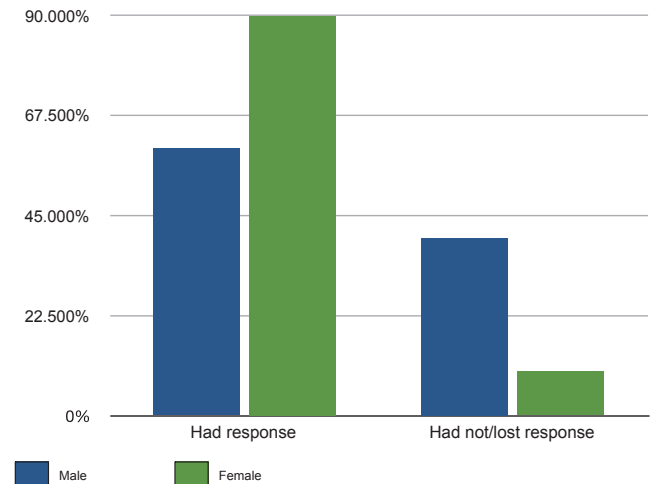


Fig. 3 – Relationship among gender and groups of patients who had or had not/lost response to anti-TNF. $p = 0.0000914$.

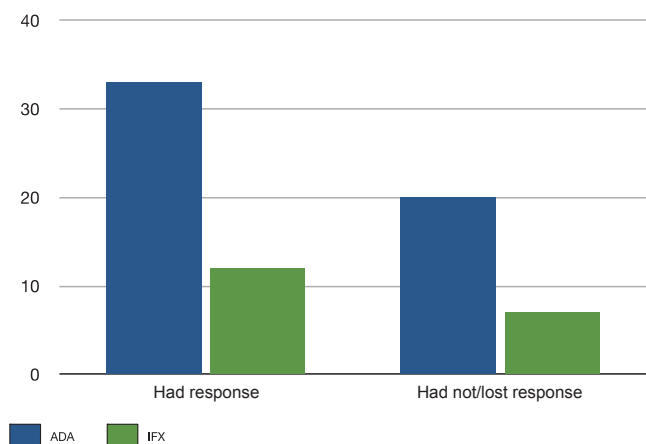


Fig. 4 – Evaluation of clinical response with respect to anti-TNF used. $p = 0.05$. ADA, adalimumab; IFX, infliximab.

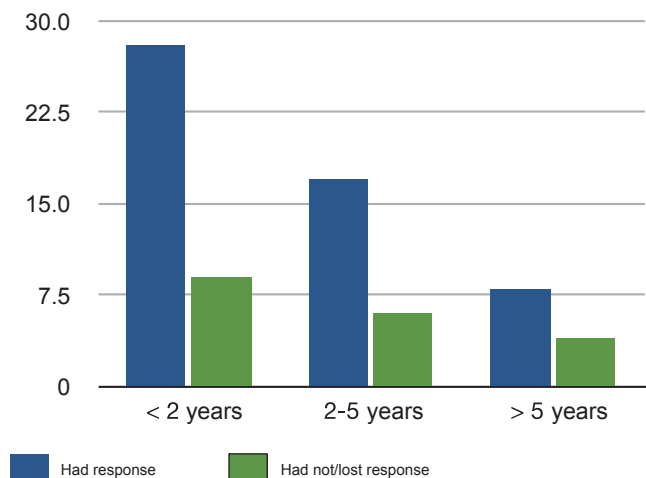


Fig. 5 – Evaluation of the interval between the onset of symptoms of DC using anti-TNF in patients who had a response and those who had not/lost response. $p = 0.003$ between <2 years and 2-5 years; $p = 0.004$ between 2-5 years and >5 years.

When we analyzed the interval between the first symptoms of AD and the beginning of biological therapy, a statistically significant difference between groups was perceived. Among those who had a clinical response, 28 (53%) initiated the use of anti-TNF with less than two years of symptoms, 17 (32%) between two and five years and eight (15%) with more than five years. Of those who did not respond/lost response, nine (47%) started treatment with less than two years of clinical manifestations, six (32%) between two and five years and four (21%) after five years (Fig. 6).

Discussion

The selection of the anti-TNF agent was based on patient preference and availability of access to hospital. A study with a larger number of patients to evaluate this criterion examined patients with rheumatoid arthritis and has shown a slight

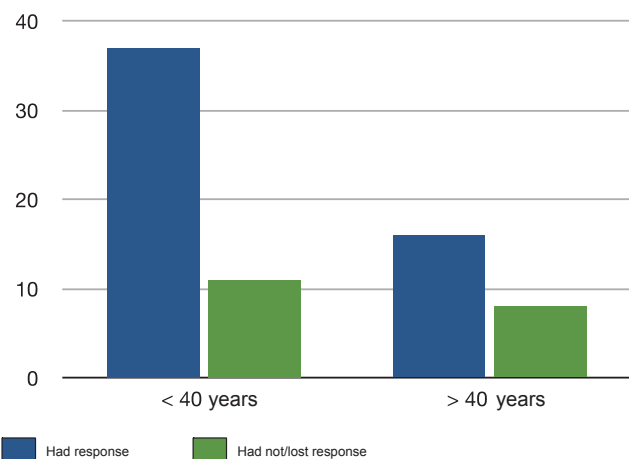


Fig. 6 – Comparison between groups that had response versus had not/lost response, with respect to age. $p = 0.0003$.

preference for the use of intravenous anti-TNF.⁶ Specifically in DC, the CHOOSE study showed a different result, with greater preference for subcutaneous anti-TNF (adalimumab, 36%, and certolizumab pego 128%), compared to 25% with preference by intravenous administration (infliximab).⁷ Vavricka et al. reported that, when questioned about the reason for the choice of subcutaneous anti-TNF, 69% of patients stated that the ease of use was determinant. In the present study it was also observed that there was a greater preference for subcutaneous anti-TNF, probably due to its greater practicality.

Since the publication of Colombel et al.³ demonstrating greater efficacy of infliximab in combination with azathioprine, it became almost mandatory to use, when possible, the so-called combotherapy to ensure improved response to anti-TNF. The authors believe that this combination can promote lower immunogenicity, so as to allow the efficacy of the drugs for a longer time, besides the very action of azathioprine, which is extremely beneficial in many cases of Crohn's disease. This has also been subsequently confirmed by other authors.⁹ In our study it was also observed that when the pharmacological combination of anti-TNF with an immunosuppressant was used, this latter drug could be kept in a larger number of patients, since 75% of patients who had a response to anti-TNF were also in use of azathioprine, against 58% of those who lost or had no response to this medication.

It seemed to us quite interesting to observe that women were more responsive than men to the use of biologicals. There is little information on this topic in the medical literature. However, in a study of gender differences in response to treatment of DC performed in children, Lee et al.¹⁰ were not able to identify differences in response to treatment with anti-TNF among boys and girls. In adults with luminal or fistulizing CD, Sprakes et al.¹¹ obtained findings opposite to our results, with male gender as a predictor of good response to IFX.

No difference in response to treatment was observed comparing patients using ADA and IFX. Kestens et al.¹² recently published a study comparing IFX and ADA in patients without prior treatment with anti-TNF; these authors also were not

able to demonstrate differences between these two agents with respect to efficacy in CD.

A better response to anti-TNF in patients less than 40 years versus older patients was observed. Weiss et al.¹³ found no difference in response to treatment with anti-TNF with respect to the age of patients in a recently published study, in which the authors analyzed the difference in response regarding age.

Currently, the time elapsed between the onset of symptoms and the treatment of DC with anti-TNF has been appreciated, because the shorter this period, the better the response to this therapeutic agent.¹⁴ The same situation was observed in the present study, because the group treated with less than two years of diagnosis obtained better results than those patients treated with a diagnosis established between 2-5 years, and this latter group obtained better results versus the group with > 5 years of diagnosis.

Conclusion

The observed characteristics of better response to treatment of DC with anti-TNF were associated with azathioprine, female gender, age < 40 years and less than two years of diagnosis.

Conflicts of interest

The authors declare no conflicts of interest.

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