Women respond better to biological therapy in Crohn’s Disease

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OBJECTIVE: Crohn’s disease is in itself a major challenge for those treating inflammatory bowel diseases. Those exhibiting the fistulizing form, particularly perianal fistulas, create even more of a challenge, as there is great difficulty in obtaining disease control even using long-term therapeutic advances made in recent years. We evaluated the difference between the gender of patients under biological treatment for Crohn’s Disease and perianal fistula.

METHODS: We studied 30 patients with Crohn’s Disease with perianal fistula with a mean age of 35 years, from 2000 to 2013. All were naïve to biological agents and received these medications in usual doses and intervals. All were also treated surgically with curettage and placement of seton-stitches prior to the use of biological agents. The results were analyzed statistically by Student’s t test, p < 0.05 being considered a significant difference.

RESULTS: Among responders, ten were men and nine were women, with no significant difference between genders in this regard. Among non-responders, eight were men and three were women: thus, significantly more men vs. women were non-responders. In general, 55% of men and 75% of women were responders.

CONCLUSION: Women exhibited a lower failure rate when exposed to biological treatment for perianal fistula in Crohn’s Disease when compared to men.

KEYWORDS: Crohn’s disease; Infliximab; Adalimumab; perianal fistula; gender.

INTRODUCTION

Crohn’s disease (CD) is in itself a major challenge for those treating inflammatory bowel diseases. Patients presenting with the fistulizing form, particularly perianal fistulas, create even more of a challenge, as there is great difficulty in controlling the disease even with the therapeutic advances for long-term treatment made in recent years1.

It is currently perceived that the best therapeutic option for this presentation of CD is the association of surgical treatment with the use of anti-tumor necrosis factor (anti-TNF) agents; by surgical treatment we do not mean classic fistulotomy or fistulectomy, but successive curettage and seton location, promoting healing without abscess formation2.

Conventional treatment of perianal fistulas in individuals without CD produce excellent results, but CD patients can not use standard techniques in most cases because they have a high probability of developing fecal incontinence. This situation could be positively changed with the emergence of biological therapeutic procedures, which significantly alter the treatment of this disease.

Relevant reports on this subject show that biological therapy can cure patients with perianal fistulae in Crohn’s disease in 30% to 40% of cases3-5.

Sands et al.3 observed that 36% of patients with CD remained without leakage after 54 weeks in response to Infliximab (IFX) use.

The CHARM study4 also demonstrated efficacy of Adalimumab (ADA) in 33% of cases of perianal fistulae at week 56, very similar to that reported in the study by Sands et al.3. The CHARM study also demonstrated that those with an initial positive response to treatment still exhibit closed fistulae over time.

However, despite some good results with these treatments, we are still far from an ideal situation; draining fistulae remain with most patients, even when using the best current therapy for Crohn’s disease.

Thus, it is necessary to find mechanisms to improve responses to anti-TNF. Maybe one of those ways is to identify characteristics of patients who respond better to therapy so that we can properly select those who will follow this line of treatment. The main objective of this study was the evaluation of gender difference for patients undergoing biological treatment for Crohn’s Disease and for perianal fistulae.

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treatment, absence of perianal purulent secretion and there was complete absence of symptoms and signs after (10 Infliximab þ (9 Adalimumab anti-TNF. Sixteen were treated with Adalimumab. Nineteen patients have received Azathioprine (AZA) plus seton stitches prior to the use of biological treatment. All were treated surgically with curettage and placement of seton stitches prior to the use of biological treatment. Nineteen patients have received Azathioprine (AZA) plus anti-TNF. Sixteen were treated with Adalimumab (9 Adalimumab + Azathioprine) and 14 with Infliximab (10 Infliximab + Azathioprine).

The outcome was considered a successful response when there was complete absence of symptoms and signs after treatment, absence of perianal purulent secretion and complete closure of the fistulous orifices. The results were analyzed statistically by Student’s t test; a p < 0.05 value was considered to be significant.

METHOD
We studied 30 patients with CD with perianal fistula with a mean age of 35 years, from 2000 to 2013. They were all naïve to biological agents and received these medications in usual doses and intervals (Infliximab 5 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter; Adalimumab 160 mg at week 0, 80 mg at week 2 and 40 mg every 2 weeks thereafter). All were treated surgically with curettage and placement of seton stitches prior to the use of biological treatment. Nineteen patients have received Azathioprine (AZA) plus anti-TNF. Sixteen were treated with Adalimumab (9 Adalimumab + Azathioprine) and 14 with Infliximab (10 Infliximab + Azathioprine).

The outcome was considered a successful response when there was complete absence of symptoms and signs after treatment, absence of perianal purulent secretion and complete closure of the fistulous orifices. The results were analyzed statistically by Student’s t test; a p < 0.05 value was considered to be significant.

RESULTS
Positive responders included 10 men and nine women (p = 0.13), with no difference between genders in this regard. Non-responders were eight men vs. three women (p = 0.03), indicating that among non-responding patients, men appear in a significantly higher proportion than women. When analyzing genders separately, we observed that of the 18 men, 10 had a response (55%), and among the 12 women, nine had a response (75%). The results are presented at Figure 1. Comparisons were performed between genders for response to anti-TNF therapy in patients with anal fistula and Crohn’s Disease.

DISCUSSION
Many aspects have been analyzed in relation to the biological response in patients with CD. Some are well documented, such as the time between the onset of the disease and early treatment. Others are still poorly studied such as the influence of gender, for example. We believe that, although the therapeutic arsenal available for perianal fistulas in Crohn’s disease is still far from ideal, these aspects should be further explored so that we can increase our effectiveness until new agents could solve this problem. This study indicates that a higher proportion of women as opposed to men with Crohn’s disease respond positively to biological plus surgical treatment.

When studying CD and Ulcerative Colitis in pediatric patients, Lee et al. observed no significant sex differences in disease severity, BMI, height or medication use. Thus the data do not support the concept of sex as a major factor in patient risk stratification for children with inflammatory bowel disease (IBD). In addition, despite concerns for sex-specific complications of some medications, their analysis did not suggest any sex differences in medication use.

This is a highly controversial subject. Another point of view is presented by Blumenstein et al. analyzing women with CD and immunosuppressive treatment. With the exception of extended disease duration in women, no significant gender-related differences in demographic and clinical characteristics were observed. Men showed a significantly higher remission rate than women, while women received significantly less immunosuppressive medication compared to men. In addition, treatment with immunosuppressant drugs was not different in women with child-bearing potential compared to menopausal women.

The authors did not evaluate biological agents in this population; however, the study shows some differences between genders that should be considered.

Sprakes et al. observed the opposite of our research. They concluded that it is unclear why males had a significantly lower likelihood of both failure to respond to Infliximab induction therapy and failure to achieve sustained clinical benefit. The majority of women who discontinued therapy did so within the first six months following Infliximab initiation, and the number of cases that discontinued each year subsequent to this were similar for both males and females. This may represent incorrect patient selection at the time of commencement of Infliximab, or reflect the fact that functional disorders, such as Irritable Bowel Syndrome (IBS), which may mimic ongoing activity in CD, are more prevalent in the female population in general.

A major concern in the treatment of women with CD is offering those in their reproductive age the ability to have children at a similar level as women without CD. Mañosa et al. analyzed a total of 503 female patients with IBD: 71% of these had a total of 659 children, 36% of whom were born after the diagnosis. A total of 132 miscarriages were registered, 46% after the diagnosis of IBD. Most childless patients stated that having no children was a personal decision, and only 6% of them were evaluated and diagnosed with infertility. Pregnancies after diagnosis of IBD had a higher probability of caesarean section and preterm delivery, but the infertility rate among IBD patients seems to be similar to that seen in the general population.

In the same sense as that of this study, Billioud et al. analyzing CD patients treated with Adalimumab, observed that more men than women were non-responders. Predictors for unresponsiveness or dose escalation were (a) male gender, (b) current/former smoker status, (c) family history of inflammatory bowel disease, (d) isolated colonic disease, (e) extra-intestinal manifestations, (f) 80/40 mg induction therapy, (g) longer disease duration, (h) greater baseline Crohn’s Disease Activity Index, (i) concomitant corticosteroid use, (j) no deep remission at week 12, (k) low serum trough concentrations of Adalimumab, (l) previous...
Infliximab non-response and (m) being previously treated with an anti-tumor necrosis factor agent.

An obvious limitation of this study is the small number of cases. However, reports with large numbers of cases specifically analyzing perianal fistulae in patients with Crohn’s disease are not common in the literature. Perhaps one of the largest reports analyzing biological efficacy in patients with CD was published in 2013, in which Panaccione et al. observed 778 patients, but of these, only 70 had perianal fistula. This study, however, did not assess differences in response to biological therapy according to gender.

Thus it should be noted that reports on the biological response in patients with CD are scarce. Other studies on the influence of gender in this response are necessary.

■ CONCLUSION

Women exhibited a lower rate of failure in response to biological treatment for perianal fistula in CD when compared to men.

■ RESUMO

OBJETIVO: A doença de Crohn é um grande desafio para o tratamento de doenças inflamatórias intestinais. Pacientes que apresentam uma forma fistulizante, particularmente com fistulas perianais, criam mais um desafio, pois há grande dificuldade em obter o controlo da doença, mesmo usando os avanços terapêuticos de longo prazo realizados nos últimos anos. Avaliou-se a diferença entre o gênero dos pacientes em tratamento biológico para a doença de Crohn e fistula perianal.

MÉTODO: Foram estudados 30 pacientes com doença de Crohn com fistula perianal, com idade média de 35 anos, 2000-2013 nunca antes tratados com agentes biológicos; receberam estes medicamentos em doses e intervalos habituais. Todos foram também tratados cirurgicamente com curetagem e colocação de “seton—stitches” antes do uso de agentes biológicos. Os resultados foram analisados estatisticamente pelo teste t de Student, \( p < 0.05 \) sendo considerado uma diferença significativa.

RESULTADOS: Entre os respondentes, dez eram homens e nove eram mulheres, sem diferença significativa entre os sexos, a este respeito. Entre os não-respondentes, oito eram homens e três eram mulheres: assim, significativamente mais homens contra as mulheres eram não-respondentes. De um modo geral, 55 % de homens e 75 % das mulheres responderam ao tratamento.

CONCLUSÃO: As mulheres apresentaram uma taxa de falha menor quando expostas a um tratamento biológico para a fistula perianal na doença de Crohn, quando comparadas aos homens.

■ REFERENCES