

Determinants of clinical response in complex perianal fistulae in Crohn's disease treated with anti-TNF α agents: A retrospective study

Fatores determinantes na resposta clínica de fístulas complexas perianais de doença de Crohn, tratadas com agentes anti-TNF α : Estudo retrospectivo

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RESUMO

Introdução: A combinação de fármacos anti-TNF α e cirurgia é a estratégia terapêutica mais eficaz nas fístulas perianais complexas da doença de Crohn.

Objetivos: Identificar fatores determinantes na resposta clínica das fístulas perianais de Crohn, em adultos.

Métodos: Estudo retrospectivo de doentes acompanhados consecutivamente numa consulta de cirurgia colorretal, de janeiro de 2010 a janeiro de 2014. Compararam-se os doentes que sob medicação anti-TNF α e cirurgia obtiveram melhoria clínica, com os que não tiveram resposta a esta terapêutica.

Resultados: De 73 adultos com doença de Crohn perianal, 59 tinham fístulas complexas. Destes, 41 (69,5%) foram tratados com fármacos anti-TNF α e cirurgia, com resposta clínica em 33 (80,5%). Comparados com estes, os oito doentes que não tiveram resposta à terapêutica apresentavam doença de Crohn mais prolongada ($p=0,038$) e menos frequentemente puderam ser submetidos a cirurgia curativa das fístulas ($p=0,001$). Destes doentes sem resposta, dois desenvolveram cancro em fístula ($p=0,34$) e três acabaram por ter indicação para proctomia ($p=0,001$). As fístulas perianais que foram primeira manifestação de doença de Crohn recidivaram ou obtiveram apenas resposta parcial, com maior frequência ($p=0,048$).

Conclusões: Quatro- quintos dos doentes de Crohn com fístulas perianais complexas tratadas com fármacos anti-TNF α e cirurgia responderam à terapêutica e foram mais frequentemente submetidos a cirurgia definitiva. A ausência de resposta esteve associada a doença de Crohn mais prolongada e a fístulas que foram manifestação inaugural da doença.

Palavras-chave: Doença de Crohn; Fístulas perianais; Cirurgia; terapêutica anti-TNF α

ABSTRACT

Introduction: The most effective strategy to treat complex perianal fistulae in Crohn's disease patients is the combination of anti-TNF α agents with surgery.

Aim: To identify determinants of clinical response of Crohn's complex perianal fistulae in adult patients.

Methods: Retrospective analysis of consecutive adult patients with Crohn's perianal fistulae followed in colorectal surgery consultation, between January 2010 and January 2014. Responders patients treated with anti-T α agents and surgery were compared with non-responders.

Results: From a total of 73 adult patients with perianal Crohn's disease, 59 had complex fistulae, 41 of which (69.5%) received treatment with anti-TNF α agents and surgery – 33 (80.5%) with an initial response to treatment while 8 had no response. The non-responders group had longer duration of CD than responders ($p=0.038$) and patients were submitted less frequently to definitive surgery for fistulae ($p=0.001$). In Non-Responders group 2 patients developed cancer in fistulae ($p=0.034$) and 3 patients needed proctectomy ($p=0.001$). Perianal fistulae as the first manifestation of CD were more likely to relapse or to respond partially ($p=0.048$).

Conclusions: Four-fifths of CD patients with complex perianal fistulae treated with anti-TNF α agents and surgery responded to treatment and had definitive surgery more frequently. Non-response to treatment was related with a longer Crohn's disease duration and with perianal fistulae as the first manifestation of CD.

Keywords: Crohn's disease; Perianal fistulae; Surgery; Anti-TNF α treatment.

INTRODUCTION

About 21-23% of Crohn's disease (CD) patients develop perianal fistulae (PF), with a cumulative frequency of 26% at 20 years.^{1,2} Prevalence of PF is influenced by the location of CD.^{1,2,3} Perianal fistulae can occur before, simultaneously or even years after the onset of intestinal symptoms.^{2,4,5,6}

Most experts classify PF as being simple or

complex, but there is no consensus regarding this matter (ECCO Statement 9E – EL5, RG D).⁷ Simple fistulae arise below the pectinate line and have one external drainage opening. Complex fistulae are located above the pectinate line and can have multiple internal and/or external drainage openings, associated abscesses, rectal stenosis or active rectal disease. Rectovaginal fistulae are also

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considered complex. Clinical assessment is effective in determining medical and surgical treatment responses (ECCO Statement 9L-EL2b, RG D).⁵

To achieve the best possible result, therapeutic approach to PF should be undertaken by a multidisciplinary team including gastroenterologists and colorectal surgeons.^{7, 8, 9, 10, 11} The most effective therapy for complex PF should combine the use of immunosuppressants, anti-TNF α agents and surgery.⁷ Antibiotics play an important role in treating local inflammation. Studies have shown that Infliximab was the first successful biological agent in induction and maintenance of fistulae closure in CD (PF were closed for more than a year).^{2, 12, 13, 14} In CHARM Trial – a 56-week phase III trial assessing the efficacy of Adalimumab as maintenance treatment, among responders to induction treatment - patients with draining fistulae at baseline, showed complete fistula healing in 33% of Adalimumab treated patients versus 13% of placebo ones. Drainage can recur if the treatment with anti-TNF α is suspended.¹⁵

Conservative surgery offers better results than a more aggressive approach.^{5, 7} Abscess drainage, setons placement, fistulotomy, LIFT technique (Ligation of Intersphincteric fistula tract), advancement flap procedures, fibrin glue and use of plugs are all surgical treatment options. The use of stem cell therapy, though still experimental, has rendered positive results.^{5, 16, 17} Proctectomy is indicated in patients with refractory disease, a damaged anal sphincter or cancer. In some cases, a diverting stoma is indicated as a bridge to other surgical procedures or in case of patient's refusal to proctectomy.⁵

AIM

To identify determinants of clinical response of Crohn's complex perianal fistulae in adult patients treated with biologic agents.

METHODS

This was a retrospective analysis of consecutive adult patients (age > 18 years) with PF in CD followed in a single colorectal surgery consultation, between January 2010 and January 2014. The study was approved by institutional Ethics Committee and Department of Education and Training. Data were collected from clinical files, respecting anonymity at all stages.

Crohn's disease and PF diagnoses were based on clinical assessment, endoscopy, endoanal ultrasound and/or magnetic resonance imaging and histopathological data from biopsies. Treatment of all patients was discussed and decided among colorectal surgeons and gastroenterologists.

Response to treatment was defined as a decrease in the number of active fistulae (50% or more), in at least two consecutive consultations, and Remission was defined as cessation of drainage by applying gentle pressure to the fistula, in at least two consecutive consultations. This clinical definition is accordant to Present et al, and conforms to the majority (59%) of the participating specialists of the ECCO Consensus of 2010.¹⁸ Among patients treated with anti-T α agents and surgery, responders (RS) group were compared with non-responders (NRS).

Statistical tests used for data analysis were t-test and chi-squared test. $P < 0.05$ was considered statistically significant.

RESULTS

Our population sample consists of 73 patients. Fifty-nine had complex fistulae, 11 had simple fistulae, 2 had anal stenosis and 1 had perianal and vulvar ulcerations and fissures. One of the patients with anal stenosis needed proctectomy with colostomy and the other was controlled with anti-TNF α therapy. The patient with perianal ulcerations and fissures achieved remission with anti-TNF α therapy.

Patients with simple fistulae

All the eleven patients with simple fistulae were treated with antibiotics and 5 of them did not receive any other medical treatment. In this group, 6 were also treated with azathioprine (> 3 months) and 2 with anti-TNF α agents. Regarding surgical procedures, 5 patients underwent a fistulotomy, 3 patients went through long-term drainage with seton(s) placement, 1 patient had both fistulotomy and seton placement and 2 patients did not undergo surgery. All of them achieved remission.

Patients with complex fistulae

Fifty-nine patients had complex fistulae, 29 male

■ TABLE 1

Data on patients with complex fistulae who received treatment with anti-TNF α agents (n=41)

	Responders (n=33)	Non-Responders (n=8)	p
Age at CD diagnosis (median)	28 years	22.5 years	0.120
Age at first PF manifestation (median)	32 years	24.5 years	0.198
PF as first manifestation of CD	22 (66.7%)	4 (50%)	0.380
CD duration (median)	11 years	14.5 years	0.038
PF duration (median)	7 years	10.5 years	0.128
Rectal disease	14 (42.4%)	6 (75%)	0.098
Anal stenosis	1 (3%)	1 (12.5%)	0.265
Abscess in disease's history	30 (90.9%)	7 (87.5%)	0.771
Carcinoma associated with fistula	0	2 (25%)	0.034
CD location, apart from perianal:			
· L1*	6 (18.2%)	2 (25%)	0.629
· L2*	4 (12.1%)	2 (25%)	
· L3*	20 (60.6%)	4 (50%)	
· perianal only	3 (9.1%)	0	
CD behavior:			
· B1*	7 (21.2%)	1 (12.5%)	0.324
· B2*	4 (12.1%)	3 (37.5%)	
· B3*	19 (57.6%)	4 (50%)	
· perianal only	3 (9.1%)	0	
Anti-TNFα agents treatment duration (median)	38 months	60 months	0.809
Surgery:			
· exclusive drainage (abscess drainage/ long term drainage - seton)	12 (36.4%)	2 (25%)	0.001
· drainage (seton) + fistulotomy or advancement flap	21 (63.6%)	3 (37.5%)	
· proctectomy	0	3 (37.5%)	

*Montreal classification for Crohn's disease.³⁰

and 30 female. Eighteen patients (30.5%) weren't treated with biological agents and, among those, 13 received purine analogues (azathioprine/6-mercaptopurine) or methotrexate and seton(s) placement. All patients were treated with ciprofloxacin and/or metronidazole and surgical procedures on different occasions during the course of the disease. Ten patients achieved clinical remission. One patient had partial response but due to psychiatric illness is not entitled to treatment with biological agents. Two patients had severe destructive disease at the time of diagnosis and were selected for proctectomy. The remaining 5 patients were only submitted to seton(s) placement or fistulotomy: 4 achieved clinical remission and 1 was submitted

to proctectomy due to destructive lesions.

Patients with complex fistulae and biologic therapy

Forty-one patients (69.5%) were treated with anti-TNF α agents and surgery (Table 1). Thirty-three (80.5%) had an initial response to treatment (RS) and 8 (19.5%) did not (NRS). Between the 2 groups of patients no significant differences were noted concerning age at CD diagnosis, age at first PF manifestation, PF as the first manifestation of CD, perianal disease duration, rectal disease, anal stenosis, abscess formation, location and behavior of luminal disease and anti-TNF α treatment duration. Three patients in the RS group had exclusive

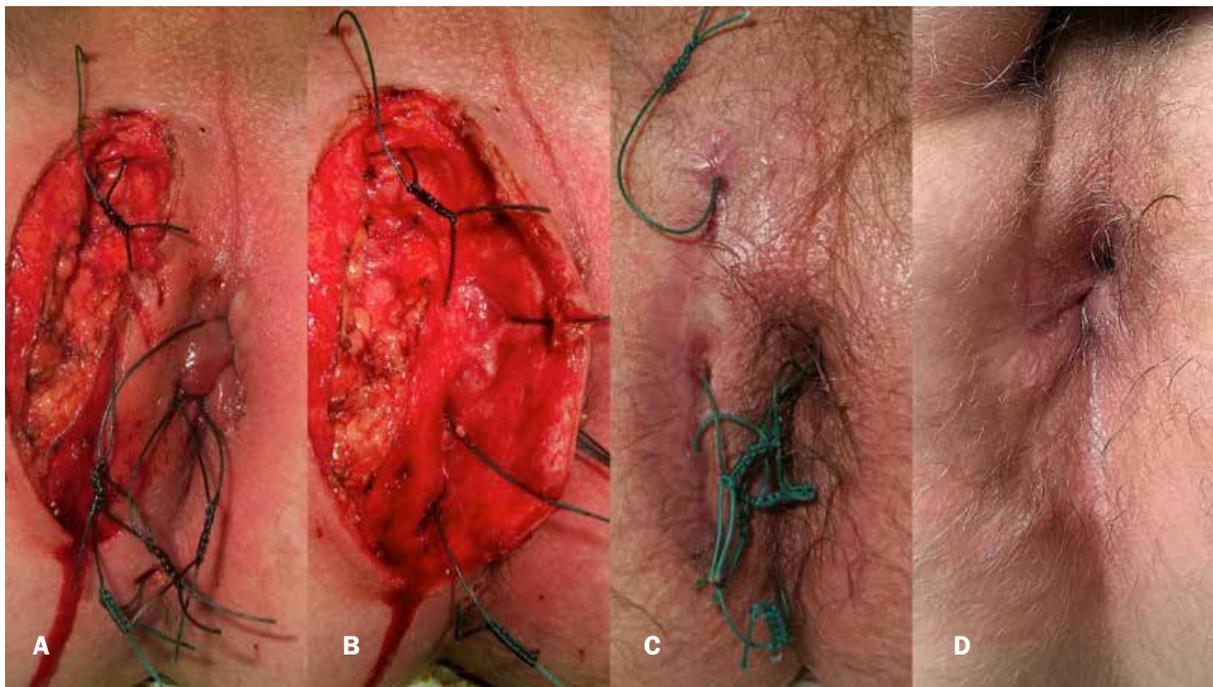


FIGURE 1. Evolution of complex perianal fistulae with drainage surgery and Infliximab therapy. The patient was 23 years old with a Montreal classification of disease A2 L1 B2p. **A** – First drainage surgery under treatment with azathioprine and antibiotics. **B** – Second drainage surgery under azathioprine and infliximab. **C** – Partial response under infliximab monotherapy. **D** – Remission under infliximab therapy.

CD perianal disease.

All 41 patients treated with anti-TNF α agents went through drainage procedures – abscess drainage and/or long-term drainage with seton(s) – which were the only surgical treatment in 25% of the NRS group and 36.4% of the RS group ($p=0.001$). Fistulotomies were performed in patients without active rectal disease with low fistulae, during or after partial/total response to treatment - evolution of 1 of these patients can be observed in Figure 1. NRS patients had longer CD duration than RS ($p=0.038$) and definitive surgical treatment of PF was less frequently applied ($p=0.001$). Proctectomy was performed in 3 NRS patients due to intractable disease ($p=0.001$). The only 2 patients who developed cancer in anal fistula were from NRS group ($p=0.034$): one died of metastatic disease and the other was treated with specific oncological therapy.

In the RS group (Table 2), 15 patients (45.5%) achieved clinical remission and 16 (48.5%) have had a partial response. Two patients relapsed after an initial clinical response; one did it after treatment interruption due to spongiotic dermatitis. Patients who had PF as the first manifestation of

disease were more likely to relapse or to respond partially ($p=0.048$). Data of the NRS group are described in Table 3.

DISCUSSION

This study is a case control (retrospective) study based on a small sample. The 2 groups of patients are matched for age at CD diagnosis, age at first PF manifestation, PF as the first manifestation of CD, perianal disease duration, location and behavior of luminal disease, rectal disease, abscess formation, concomitant anal stenosis, and duration of anti-TNF α treatment.

Perianal CD often predicts aggressive forms of overall CD.¹⁹ The best therapeutic strategy for PF in CD is the association of medical and surgical treatment and a multidisciplinary team should run therapeutic decisions.²⁰ Perianal manifestations become gradually more common as the disease is located more distally in the colon.¹ Active proctitis increases the risk of having PF and also predicts the higher probability of treatment failure and disease recurrence.^{7,18} In this study, patients with rectal disease were more likely to be NRS, despite not

■ TABLE 2

Data of the patients who were responders to anti-TNF α treatment

	Remission (n=15)	Partial Response (n=16)	Relapse (n=2)	p
Age at CD diagnosis (median)	29 years	26 years	36 years	0.951
Age at PF first manifestation (median)	33 years	28.5 years	36.5 years	0.553
PF as first manifestation of CD	7 (46.7%)	14 (87.5%)	1 (50%)	0.048
CD duration (median)	12 years	7.5 years	17.5 years	0.317
PF duration (median)	6 years	7 years	17 years	0.190
Rectal disease	7 (46.7%)	6 (37.5%)	1 (50%)	0.854
Anal stenosis	0	1 (6.2%)	0	0.578
Abscess	14 (93.3%)	14 (87.5%)	2 (100%)	0.767
Duration of anti-TNF α agents treatment (median)	30 months	46.5 months	80 months	0.471
Surgery:				
· exclusive drainage (abscess drainage/seton)	7 (46.7%)	5 (31.2%)	0	0.366
· seton + fistulotomy or advancement flap)	8 (53.3%)	11 (68.8%)	2 (100%)	

■ TABLE 3

Data on the group of non-responders to anti-TNF α treatment

Patients (n=8)	Anti-TNF α agents treatment (months)	Notes
1	12	Regular treatment was not fulfilled
3	50 (median)	Proceeded to proctectomy
2	96 (median)	Fistulae-associated carcinoma
2	61 (median)	Anti-TNF α agents were maintained for luminal disease

reaching statistical significance. This might be due to insufficient statistical power and a larger cohort could perhaps confirm this fact. Disease location and behavior were not significantly related to treatment response.

Régimbeau *et al*²¹ found an association between PF as the first CD manifestation and a poor prognosis, with greater likelihood of proceeding with abdominoperineal resection. In this series, PF as the first manifestation of CD has been shown to have a significant negative impact on prognosis: in the RS group, this particular presentation had

a lower remission rate and higher rates of partial response or relapse.

There are no consistent predictors described in literature, to identify patients prone to treatment failure.²² It is known that treatment is less effective in complex perianal disease^{18,26} and that biological therapies has led to great improvements in PF management.²³ Medical treatment of complex disease should include antibiotics, immunosuppressants and anti-TNF α agents.⁸ Infliximab and Adalimumab are moderately effective induction and maintenance of fistula closure²⁴ and, to achieve better results, anti-

TNF α should be started as soon as symptoms emerge.¹³ Although based on a small sample, we observed that most patients with complex fistulae treated with anti-TNF α and surgery (80.5%) responded to treatment and that 45.5% of these ones remained in clinical remission. Patients with longer duration of CD had significantly less improvement with treatment.

Despite the general use of Metronidazole and/or Ciprofloxacin for treating PF in CD, there are no controlled trials concerning their efficacy. However, several studies show PF recurrence once

antibiotics are suspended.^{8,16} All patients included in our study were given antibiotics on different occasions during the course of perineal disease. To avoid septic complications and to optimize pharmacologic therapy results, it is essential to perform surgery before or during anti-TNF α therapy.¹⁸ When combining Infliximab with curettage and seton placement one can achieve a better and longer response and lower recurrence rates.^{13, 25, 26,}

²⁷ Definitive surgical treatment was more likely to be performed in the RS group.

Weiss *et al*²⁸ found no difference in treatment response with anti-TNF α regarding patient's age. In the literature there is little information concerning gender and treatment response²¹ and in this series there were no significant associations between gender and age and treatment response. Proctectomy is the last option to improve quality of life in patients with destructive PF and is performed in up to 25% of patients.²⁹ In this series, 3 of the 41 patients (7.3%) with complex fistulae treated with anti-TNF α agents needed a proctectomy, and all of them were NRS ($p=0.001$). The increased risk of rectal and anal cancer in CD patients with active rectal disease and severe chronic PF is well known.³⁰ A refractory perianal lesion must always raise suspicion of carcinoma in fistula tracts.²⁰ In this series, two patients developed anal cancer and they were NRS ($p=0.034$). This emphasizes the need for active cancer screening in the presence of any change or worsening of clinical symptoms in long-standing and refractory perianal disease. Examination under anaesthesia with repeated biopsies and radiological investigation - MRI combined with T2 imaging - are highly recommended in this setting.³¹

CONCLUSIONS

In this small study, four-fifths of CD adult patients with complex perianal fistulae treated with anti-TNF α agents and surgery responded to treatment. These patients had a shorter duration of CD and they were more likely to be submitted to definitive surgery than non-responders ones. Perianal fistulae as the first manifestation of CD were related with lower remission rate and higher partial response or relapse rates. Non response to treatment was associated with a longer du-

ration of CD, PF as the first manifestation of CD, occurrence of cancer-in-fistulae and need of proctectomy. ■

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