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Randomized Controlled Trials in Perianal Crohn's Disease

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Abstract: Crohn's disease can be complicated by the development of fistulas, 54% of which involve the perianal region. The presence of perianal fistulas predicts a disabling course of Crohn's disease.

The treatment of complex perianal disease is difficult and the chance of complete fistula healing is no more than 50%. The best management of this condition is a combining medical and surgical therapy. Studies which evaluated the efficacy of medical treatments in this setting are small, open label and considered the efficacy on perianal disease as a second outcome or as the result of a subgroup analysis. In the few available trials the efficacy outcomes were evaluated by the Fistula Drainage Assessment but recently it was observed that inflamed fistula tracks often persist, despite the apparent closure of external orifices.

Up to now the most strongly evaluated medical treatments for perianal Crohn's disease are the anti-TNFα antibodies. In presence of complex fistulas they are considered the first choice of medical treatment, in combination with surgical therapy. Antibiotics and immunomodulators have not been demonstrated to result in sustained closure of fistulas in Crohn's disease. Their use is recommended as a second line medical treatment. The use of tacrolimus and thalidomide is limited by its side effects. A few evidences support the use of methotrexate and cyclosporine but they are insufficient.

Keywords: Perianal disease, fistula, Crohn's disease, infliximab, adalimumab, surgery, trials.

INTRODUCTION

Crohn's disease (CD) is characterized by a transmural inflammation of the bowel, which can lead to the development of fistulas in 17% to 43% of the cases [1,2]. It is possible to recognize four types of fistulas: enterocutaneous, enteroenteric or enterocolic, enterovaginal and enterovescicular. A cumulative incidence of fistulas of 33% after 10 years and 50% after 20 years from diagnosis was reported [3]. Of these fistulas, 54% involve the perianal region. The presence of perianal disease is considered an independent factor predicting a disabling course of CD [4]. Since these fistulas often involve the anal sphincters, they can be a source of significant morbidity, with an increased risk for incontinence in case of complex fistulas, which may require an aggressive surgical intervention.

The treatment of perianal CD is still very difficult, achieving healing is a long process and a recurrence rate of 20 % was reported after surgical treatment [5-8]. Proctectomy could be required because of refractory disease or complications. Many studies evaluated the efficacy of medical treatments, alone or in combination with surgical procedures, to improve the outcomes in this subgroup of CD patients. Most of these studies are small, open label and considered the efficacy on perianal CD as a second outcome or as the result of a subgroup analysis. Few RCTs are available on treatments for perianal CD and in all of them the efficacy outcomes were evaluated by the Fistula Drainage Assessment. A fistula was considered opened if the investigator can express purulent material from the fistula with the application of gentle pressure. Fistula response was defined as closure of at least 50% of fistulas for at least 4 weeks. Complete fistula closure was defined as closure of all fistulas for at least 4 weeks. Recently was observed that inflamed fistula tracks often persist, despite the apparent closure of external orifices, causing recurrent fistulas and pelvic abscesses. Based on this observation radiological outcomes, especially using MRI examination, have been considered with promising results.

In presence of perianal disease the choice of medical, surgical or a combination of both medical and surgical treatment is determined by the type of fistula and the degree of rectal inflammation.

Based on the recent published Italian guide lines [9] on the use of anti-TNFα, in case of complex fistulas "cone-like" fistulectomy of each fistula tract should firstly be performed with sparing of sphincteric structures. Seton placement should be recommended, the timing of removal depending on subsequent therapy. Anti- TNFα agents should be used as the first choice of medical therapy, in combination with surgical therapy. Antibiotics and/or immunosuppressants should be used as a second line medical treatment. This recommendations are different from that reported in the ECCO guide lines [10], in which anti- TNFα agents are considered as second line options after antibiotics and immunosuppressants

We analyzed the more recent RCTs in which the efficacy of different drugs (antibiotics, immunosuppressants, tacrolimus and anti-TNFα) has been evaluated.

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ANTIBIOTICS

Antibiotics have been proposed for the treatment of fistulising CD for both their anti-septic and anti-inflammatory properties. The most common used antibiotics are metronidazole, at the dosage of 750 - 1000 mg daily and ciprofloxacin, at the dosage of 1000 - 1500 mg daily.

Multiple studies, most of which open-label case series involving few patients [11-13], have been performed with only modest results.

A RCT was presented comparing the efficacy of ciprofloxacin and metronidazole on perianal fistulas [14]. Twenty-five patients were randomized to receive ciprofloxacin (500 mg), metronidazole (500 mg), or placebo twice daily for 10 weeks. The primary outcome was considered the closure of all open actively draining fistulas. The closure of a fistula was defined as the absence of drainage, both spontaneous and on gentle compression. The closure of all fistulas at week 10 occurred in 3 patients (30%) treated with ciprofloxacin, no patients (0%) treated with metronidazole, and 1 patient (12.5%) treated with placebo (p= 0.41). This small study suggested that remission occurred more often in patients treated with ciprofloxacin, but the differences were not significant.

A RCT [15] was also conducted to evaluate the effect of combined ciprofloxacin and infliximab treatment in perianal CD. Twenty-four patients, treated with infliximab (5 mg/kg) at week 6, 8 and 12, were randomly assigned to receive ciprofloxacin (500 mg) twice daily or placebo for 12 weeks.

The closure of perianal fistula was defined as no drainage despite firm finger compression.

At week 18 the response rate was 73% in the ciprofloxacin group and 39% in the placebo group (p = 0.12). Using logistic regression analysis patients treated with ciprofloxacin tended to respond better (OR = 2.37, p = 0.07). The use of logistic regression analysis in this type of study is methodologically questionable.

A limit of the antibiotic treatment is the adverse events commonly associated with the long term therapy. They can include: glossitis, nausea, sensory neuropathy, headache, diarrhoea and rash.

To avoid the systemic side effects of antibiotic treatment the potential efficacy of metronidazole 10 per cent ointment has been evaluated in a RCT [16]. Seventy-four patients with perianal fistulas were randomized to metronidazole ointment, applied perianally three times daily, or placebo ointment. At the end of the study more subjects in the metronidazole group showed a reduction in perianal discharge and in perianal pain but a significant difference with placebo was not showed. The authors concluded that topical treatment with metronidazole is well tolerated, with minimal adverse effects, and could be useful for the treatment of the pain and discharge associated with perianal CD.

IMMUNOSUPPRESSANTS

There are no controlled trials where the efficacy of immunosuppressants in fistulizing CD was considered as a primary end point. The efficacy of azathioprine (AZA) and 6-mercaptopurine (6MP) in this setting was analysed in several trials where the treatment of perianal disease was considered as a secondary endpoint. Because of the small sample size of these studies a meta-analysis was conducted to have a more reliable result on the efficacy of immunosuppressants in the treatment of perianal CD. The meta-analysis of these trials [17] found that 54% of patients with perianal disease who received AZA/6MP responded versus 21% of patients who received placebo (odds ratio 4.44 [CI, 1.50 to 13.20]). The limits of these studies were the small number of analyzed patients and being not designed primarily to look at the effect of the treatment on perianal fistulas but on active inflammatory disease. The relatively low reported remission rates, with high recurrence rates, represent probably the reason for the lack of new trials focused on these drugs in favour of much more evidences on other new treatments.

TACROLIMUS

The efficacy of tacrolimus in the treatment of perianal CD has been studied in some trials.

In an old RCT [18] 42 patients with perianal fistulas were treated with tacrolimus (0.2 mg/kg daily) or placebo for 10 weeks. The fistula closure was defined as the absence of either spontaneous drainage or the ability to express drainage with gentle compression. In the tacrolimus group 43% of the patients reached the closure of at least 50% of fistulas for longer than 4 weeks, compared with 8% of the patients treated with placebo (p = 0.004). Complete fistula closure, however, was only achieved in 10% of the patients who received tacrolimus. The authors observed that fistula closure was not affected by the concomitant immunosuppressive therapy with AZA/6MP (38% closure with therapy versus 50% without).

Despite the encouraging results, a limit of the treatment with tacrolimus is represented by the high rate of adverse events, including headache, insomnia, elevated creatinine, paraesthesia, and tremor.

To avoid these systemic adverse events the efficacy of a treatment with topical tacrolimus was investigated in a RCT [19]. Nineteen patients were stratified according to whether they had ulcerating (7 patients) or fistulising (12 patients) disease and randomized to topical tacrolimus (1 g ointment twice a day) or placebo for 12 weeks. In the subgroup of patients with fistulising CD, the complete response was defined as clinical evaluated cessation of drainage of all fistulas, maintained until the end of the treatment period or for 2 consecutive visits. At the end of the study 3 of the 4 patients treated with topical tacrolimus for ulcerating disease improved, compared with none of the 3 patients in the placebo group, but a complete healing was not achieved. In fistulising disease topical tacrolimus resulted to be not effective. Adverse events were infrequent and mild. The results of this study suggest that topical tacrolimus could be effective and safe in the treatment of perianal ulcerating CD, but not of fistulising CD.

INFLIXIMAB

Infliximab has been proven to be efficacious in the treatment of fistulas in patients with CD.

The first data on its efficacy come from a trial published in 1999 [20]. In this study 94 patients with fistulising CD (85 of whom with perianal fistulas) were randomly assigned to receive infliximab or placebo at weeks 0, 2, and 6. A fistula was considered to be closed when it no longer drained despite gentle finger compression. At the end of the study 55% of the patients assigned to 5 mg/kg of infliximab had a closure of all fistulas, compared with 13% of the patients assigned to placebo.

Some years later a controlled trial (ACCENT II) [21] demonstrated the superiority of infliximab (36%) compared with placebo (19%) in maintaining a long-term healing of fistulas. In this study the response was defined as a reduction of at least 50% from base line in the number of draining fistulas at consecutive visits four or more weeks apart. A complete response was defined as the absence of draining fistulas.

It is important to underline that in these two large trials 11% and 15% of the treated patients developed abscesses related to their fistulas during the study, probably because of an early closure of the cutaneous opening of the fistula tract. To minimize this complication a combined surgical and medical treatment was proposed. Some small studies [22-26] reported a better response (from 47% to 100%), a lower recurrence and a longer time to recurrence rates in patients who had placed a seton prior to infliximab infusions compared with patients receiving infliximab alone. The more recent trials focused on the efficacy of this combined treatment.

Recently a prospective Italian study [27] was conducted to compare the outcomes of the management of perianal fistulas in CD between infliximab, surgery or a combination of surgery and infliximab. Thirty-four patients with complex perianal fistulas were included into 1 of the following 3 treatment groups: infliximab (11 patients), surgery (10 patients) or a combination of surgery and postoperative infliximab (14 patients). Patients who received surgery and infliximab experienced a shorter time to healing of fistulas and a longer mean time to relapse compared to those who received infliximab or surgery alone. This is the only RCT in which the combination therapy (medical + surgical) was compared with the classic approach (medical or surgical).

Although the initial response to infliximab resulted to be very good, the median duration of fistula closure is approximately 3 months and repeated iv infusions are often required. However, it is known that after discontinuation of infliximab therapy most fistulas recurred. Which is the best maintaining treatment for fistulising CD after infliximab and what is the best time to stop the treatment is up to now a question. New trials focused on these topics are warranted.

ADALIMUMAB

The first data on the efficacy of adalimumab in the treatment of perianal CD come from a sub-group analysis of a large trial [28] in which 117 patients with perianal disease were treated with adalimumab at the induction dosage of 80/40 mg at weeks 0/2 and then randomized to placebo, adalimumab every other week or adalimumab every week. The closure of fistulas was assessed draining upon gentle compression. Complete fistula closure was achieved in a greater percentage of adalimumab treated patients versus those receiving placebo at both week 26 (30% and 13% for combined adalimumab groups and placebo group, respectively) and week 56 (33% and 13% for combined adalimumab and placebo group, respectively). Of patients with complete fistula closure at week 26, 100% continued to have a complete fistula closure at week 56.

To evaluate the long term efficacy of adalimumab in the healing of draining fistulas, the patients completing week 56 were then enrolled in an open-label extension [29]. Of all patients with healed fistulas at week 56, 90% maintained healing after 1 year of open-label adalimumab therapy. The authors concluded that adalimumab therapy is not only effective for inducing fistula healing, but a complete fistula healing is sustained for up to 2 years by most patients.

The available data on the efficacy of adalimumab in fistulising CD are still insufficient because they come from post-hoc analyses of RCTs. New RCTs where closure of fistulas will be the major endpoint are warranted.

CERTOLIZUMAB PEGOL

Certolizumab pegol was approved for the treatment of CD in America and in Switzerland, but not in the other European countries. Data on its efficacy in the treatment of perianal CD come from sub-group analysis of large trials. Studies focused on the efficacy of this drug in perianal CD are not available. In a subgroup analysis of the PRECISE 2 trial [30] the efficacy of maintaining treatment with certolizumab pegol in fistulizing CD was evaluated. In the PRECISE 2 trial patients with draining fistulas had received an open-label induction with certolizumab pegol 400 mg at weeks 0, 2 and 4. At week 6 responders with draining fistulas had been randomised to certolizumab pegol 400 mg or placebo every 4 weeks. Fistula closure was defined as the absence of drainage on gentle compression at any two consecutive visits. At week 26, 36% of patients in the certolizumab pegol group had 100% of fistula closure compared with 17% of patients in the placebo group ($p = 0.038$).

A prospective phase IV study [31] evaluating the efficacy and safety of certolizumab pegol in a multicentre cohort of CD patients was recently published. Sixty patients were included, 53% of whom had stricturing or penetrating disease. In the sub-group of patients with perianal disease a complete fistula closure was observed in 36% of patients at week 6 and in 55% of patients at week 26. These results are promising but not still sufficient to consider certolizumab pegolas a good treatment for perianal CD. New trials are warranted.

CONCLUSION

The treatment of complex perianal CD is difficult and the chance of complete fistula healing remains no more than 50%. It is now clear that the best management of this condition is a combining medical and surgical therapy. Up to now the most strongly evaluated medical treatments for perianal CD are the anti-TNFα antibodies. Regarding the other medical treatments, antibiotics and immunomodulators have not been demonstrated to result in sustained closure of fistulas in

Table 1. Results of the Trials on Fistulising CD

Study	Investigated Drug	N° of Patients	Follow up (weeks)	Rate of Remission in Treated Patients (%)	Rate of Remission in Placebo Arm	Outcome Definition
West 2004* [15]	Ciprofloxacin + infliximab	24	18	73	39	no drainage despite finger compression.
Thia 2009 [14]	Ciprofloxacin/ metronidazole	25	10	30/0	12.5	absence of drainage, both spontaneous and on gentle compression.
Sandborn 2003 [18]	Tacrolimus	42	10	10	8	absence of either spontaneous drainage or the ability to express drainage with gentle compression.
Hart 2007 [19]	Topical tacrolimus	19	12	0	0	Drainage cessation of all fistulas, maintained until the end of the treatment period or for 2 consecutive visits.
Present 1999 [20]	Infliximab	94	2-6	55	13	no drainage despite gentle finger compression.
Sands 2004 [21]	Infliximab	306	54	36	19	Drainage cessation of all fistulas, maintained until the end of the treatment period or for 2 consecutive visits.
Colombel 2006 ** [28]	Adalimumab	117	56	33	13	no drainage despite gentle finger compression.
Schreiber 2011*** [30]	Certolizumab pegol	58	26	36	17	absence of drainage on gentle compression at any two consecutive visits.

`* Only response rate was considered
** Subgroup analysis of CHARM study
*** Subgroup analysis of PRECISE 2 study

CD. The use of tacrolimus is limited by its side effects and the efficacy of topical treatment seems to be confined to perianal ulcerating CD. The results of discussed RCTs are reported in Table **1**.

In some small, open-label studies the efficacy of other drugs have been analysed. For example patients treated with thalidomide demonstrated a significant improvement on their perianal disease in short term follow up, but the long term treatment is limited by its toxicity [32-34]. A few evidences, from small case series, are also available to support the use of methotrexate, alone [35] or in combination with infliximab [36]. Based on the results of uncontrolled small studies, an improvement in fistula drainage was observed in 3/4 of

patients treated with ev cyclosporine (4 mg⁄kg), but most patients relapsed after transition to oral therapy or discontinuation of the drug [37-39]. It has recently been suggested the potential benefit of local injection of infliximab and adalimumab, associated with surgical procedure in patients who have an intolerance to systemic treatment. Also the data on this type of treatment come from small studies [40-42].

Recently an alternative treatment with stem cell local injection was proposed for the treatment of perianal fistulas. In 2 studies [43,44] the efficacy and safety of stem cell-based therapy with expanded adipose-derived stem cells were evaluated, with promising results. In a more recent study [45] the efficacy and safety of intrafistular injections of autologous bone marrow-derived mesenchymal stromal cells were analysed and complete closure of fistula tracks was reported in 70% of patients without any adverse effects. These preliminary results are encouraging but RCTs are warranted to assess the real efficacy of cellular therapy in CD complicated by perianal fistulas.

The efficacy of oral spherical adsorptive carbon was also evaluated in recent years. In a RCT [46] 57 patients with CD and active anal fistula were assigned to receive oral spherical adsorptive carbon or placebo for 8 weeks. The reported remission rates were 29.6% in the oral spherical adsorptive carbon group and 6.7% in the placebo group (p= 0.035).

Up to now some questions remain unanswered: how to treat patients who do not respond to biologic treatments, which is the best strategy from long term maintenance therapy in responders, which is the best evaluation instrument in future RCTs on perianal CD, considering the limits of the old used Fistula Drainage Assessment?

Regarding the medical treatments we expect further RCTs to improve the management of these CD patients. Regarding the evaluation instrument, as therapy outcome resulted to be worse among patients with persisting fistulas in the MRI evaluation, despite a good Fistula Drainage Assessment, we think that MRI examination could be considered as a more reliable evaluation instrument to use in future RCTs on perianal CD.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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