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Invited Review

Role of infliximab in the treatment of fistulizing Crohn's disease

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INTRODUCTION

Crohn's disease (CD) is characterized by a chronic, granulomatous, transmural inflammation that can affect the entire gastrointestinal tract with a discontinuous pattern. During the last decades the prevalence of CD has increased in Western countries and mainly young patients are affected, with a peak incidence between the ages of 15 and 35 years.[1] Three patterns of disease behavior in the presentation of CD are recognized: perforating (fistulizing), fibrostenotic (stricturing) and nonperforating-nonstricturing (inflammatory). Various subgroups of CD patients may express predominantly one of the above-mentioned types of the disease.[2]

Fistulizing CD (FCD) is the result of the transmural inflammatory affection of the bowel wall and indicates that the inflammation has penetrated into adjacent organs, tissue, or skin. The medical treatment of patients with FCD is based on the use of antibiotics, immunosuppresants and recently of biologics, mainly infliximab. Antibiotics, cyclosporine, methotrexate and thalidomide have been used in uncontrolled trials; only azathioprine, 6-mercaptopurine and infliximab have been assessed in double blind, placebo controlled studies.[3]

The reproducibility of the pathogenetic role of TNF-α in CD as well as in various animal models of chronic colitis, together with the availability of modern biomedical techniques, made possible the development and testing of anti-TNF strategies for treatment, such as the chimeric anti-TNF-antibody infliximab.[4] During the last decade infliximab has been proved to be an effective treatment in refractory luminal CD and FCD.[15,36]

The aim of this review is to summarize the recent evidence of the role of infliximab in the treatment of FCD. Special attention will be given to the current guidelines of the appropriate administration of infliximab in FCD.

Fistulizing CD

A predominant feature of FCD is fistulae. These are either external, terminating on the body surface, like in the perianal region and the enterocutaneous fistulae or are internal, between parts of the small and/or large intestine or between the intestine and contiguous tissues and organs such as mesentery, the stomach, the bladder or the vagina. Perianal fistulae are classified as intersphincteric, transsphincteric, suprasphincteric, extrasphincteric and superficial according to the Parks classification, which uses the external sphincter as a central point of reference.[6] Furthermore a perianal fistula is classified as simple or complex according to its anatomic position, number of external openings and accompanying symptoms.

The lifetime risk for developing fistulae in patients with CD has been reported to be between 20 and 40% in referral-center cohorts.[7-9] On the other hand in a population-based study from Sweden the natural history of perianal fistulae was examined and a cumulative incidence of 23% in a period of 20 years was found.[10] Another study from US analyzed all types of fistulae and a cumulative risk of 33% after 10 years and 50% after 20 years was documented.[11] Perianal fistulae were the most common (55%). The second commonest were the entero-enteric fistulae (24%). There was a relatively high number of patients (45%) who developed a fistula at or before the diagnosis of CD. Most fistulizing episodes (82%) required operations. Furthermore, only 34% of patients developed recurrent fistulae. Finally the cumulative frequency of perianal fistulae in children and adolescents with CD was reported to be 13% at a referral center.[12]

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The treatment of fistulae in CD depends on several parameters such as location, severity of symptoms, number, the history of previous local surgical procedures and sphincter function. Therefore, it is not surprising that there is no general standard treatment. However, the appropriate integration of medical and surgical treatment is essential for the optimal management of patients with fistulae. Regarding the medical therapy, only a few studies have focused on the efficacy of various treatments in healing the fistulae in CD specifically and, to date, there has been no well-accepted fistula disease activity index for the assessment of treatment response.[13] Aminosalicylates, which are used for CD, have been proved ineffective and the use of corticosteroids seems to be detrimental in FCD.[14,15] On the other hand in several uncontrolled studies an efficacy of metronidazole in perianal FCD has been demonstrated.[16-19] However, the recurrence rate after discontinuation of metronidazole is up to 78% within 4 months and long-term administration of metronidazole is associated with an unacceptably high risk of neurotoxicity and paresthesias. Similarly, the efficacy of ciprofloxacin either alone or in combination with metronidazole has been reported to be rather unsatisfactory for long-term administration, in some small-uncontrolled studies.[20,21]

The efficacy of 6-mercaptopurine, a key metabolite of the immunosuppressive drug azathioprine, was important when the treatment of fistulae in CD was analyzed separately (response rates of 55 vs 24% in the placebo group).[22] A meta-analysis as well as other uncontrolled trials showed similar results.[23-25] The mean time to response was over 3 months and up to 8 months, suggesting a delayed mechanism of action. Furthermore a randomized placebo-controlled study on the use of oral tacrolimus (FK506) for the treatment of perianal and enterocutaneous fistulae in patients with CD showed effectiveness for fistula improvement but not fistula closure in perianal CD.[26] For other immunosuppresants including cyclosporine A, methotrexate and mycophenolate mofetil, reports on their efficacy in FCD are either anecdotal or refer to uncontrolled case series. Uncontrolled case reports and case series exist also for other medical therapies including elemental diet, bowel rest with total parenteral nutrition, thalidomide, granulocyte colony-stimulating factor and hyperbaric oxygen.

Infliximab and fistulizing CD

There is ample evidence that the mucosal inflammatory process in CD results from disproportionate activation of the T-helper 1 (Th-1) subclass of lymphocytes.[27,28] Activated Th-1 cells produce numerous cytokines including tumor necrosis factor alpha (TNF-α). Expression of these Th-1 type cytokines has been shown to be correlated with relapse and remission in CD and TNF-α, in particular, is known to stimulate mucosal inflammation.[29,30]

Infliximab is a chimeric monoclonal immunoglobulin-G1 antibody with high affinity and specificity for recombinant and natural human TNF-α. Initially it has been raised in mice. Genetic engineering techniques were used to replace the murine constant regions with their human equivalents while retaining the murine antigen-binding regions. The resulting mouse-human chimeric antibody has reduced immunogenicity and improved pharmacokinetics in humans.[31] Infliximab neutralizes the functional activity of TNF-α by blocking it from binding to the p55 and p75 TNF receptors on mucosal lymphocytes.[32] It also binds transmembrane TNF-α expressed on activated Th-1 lymphocytes leading to cytotoxic cell killing.[33] Additionally infliximab induces apoptosis of activated mucosal T-cells,[34] fixes the complement[33] and inhibits production of granulocyte-macrophage colony-stimulating factor by mucosal T-cells.[35]

Infliximab has been proved to be effective in inducing and maintaining response in patients with moderate to severe luminal CD refractory to conventional therapy.[4,5] It has also been shown to have a steroid-sparing effect. Similarly it represents the only medical treatment that has been proved efficacious in FCD.[36,37] Despite the relatively high cost of drug acquisition, preliminary pharmacoeconomic analysis indicates that infliximab is cost effective compared with existing treatments.[38] In contrast with azathioprine and methotrexate, infliximab acts rapidly when given during an FCD flare.

The first randomized, double blind, placebo-controlled study which was conducted by Present *et al*[36] focused on CD patients with enterocutaneous fistulae. A total of 94 patients with either draining abdominal fistulae (10% of patients) or perianal fistulae (90% of patients) were treated with 5 mg/kg body weight infliximab, 10 mg/kg body weight infliximab or placebo at weeks 0, 2 and 6. Of the patients, 68% receiving 5 mg/kg infliximab and 56% receiving 10 mg/kg infliximab achieved a closure of at least 50% of open draining fistulae compared with 26% response in patients receiving placebo ($p=0.002$, $p=0.02$ respectively – primary end point). In addition, 55% of the patients treated with 5 mg/kg and 38% of the patients treated with 10 mg/kg showed a closure of all draining fistulae vs 13% of the placebo group ($p=0.001$, $p=0.04$ respectively – secondary end

point). The median time to the onset of a response was shorter among patients treated with infliximab (two weeks) than among those given placebo (six weeks). However, the median duration of response was approximately three months in patients who reached the primary end point. Finally the beneficial effect of infliximab did not appear to be dose-related; patients treated with 5 mg/kg had a higher rate of response than those treated with 10 mg/kg.[36]

A recent multicenter follow-up study (ACCENT II) focused on whether repeated infusions of infliximab every 8 weeks are efficacious and safe in maintaining closure of draining fistulae among patients who had a response to a three-dose induction regimen of infliximab.[37] A total of 282 patients with enterocutaneous and/or perianal fistulae participated in the study. They were initially treated with a three-dose regimen of infliximab at weeks 0, 2 and 6 and those who achieved a closure of at least 50% of draining fistulae from baseline, were randomized to receive either 5 mg/kg infliximab or placebo every 8 weeks (at weeks 14, 22, 30, 38 and 46) and were followed until week 54. The remaining 87 patients, who had no initial response to infliximab administration, were also randomly assigned to receive placebo maintenance or infliximab maintenance. After 54 weeks, 36% of patients from those who had initially responded to infliximab treatment and were randomized to the infliximab maintenance subgroup still had complete absence of draining fistulae vs 19% in the placebo maintenance subgroup ($p=0.009$). The median time to the loss of response was 40 weeks in the infliximab maintenance subgroup compared with 14 weeks in the placebo maintenance subgroup ($p<0.001$). On the other side, concerning the patients who had no initial response to infliximab, 21% of the infliximab maintenance subgroup had at least partial response vs 16% in the placebo maintenance subgroup ($p=0.6$) (37). A further subgroup-analysis showed that the patients receiving infliximab as maintenance therapy had significantly fewer mean hospitalization days (0.5 vs 2.5, $p<0.05$), mean numbers (per 100 patients) of hospitalizations (11 vs 31, $p<0.05$), all surgeries and procedures (65 vs 126, $p<0.05$) and major surgeries (2 vs 11, $p<0.05$) compared with those who received placebo maintenance.[39]

Although from these carefully designed studies very promising results are provided and infliximab is currently used in the clinical practice for the treatment of FCD, every specialist must be conserned about some important issues that arise from the use of infliximab.

First of all, we have to deal with a relatively high rate of abscess formation, which is caused because of the closure of the external opening of the fistula before the internal tract has healed, due to the rapid action of infliximab. In the original trial of Present *et al,*[36] 11% of the patients treated with infliximab developed perianal abscesses in the course of their treatment, compared with only 3% of those treated with placebo. Another problem is that the cessation of infliximab induction therapy, is followed by a high rate of recurrent drainage of fistulae and this situation suggests that infliximab suppresses the inflammatory factors associated with disease activity and fistula drainage but may not eradicate the epithelialized tracts. That means that most fistula tracts persist morphologically despite clinical remission. These findings have been shown in several follow-up studies using magnetic resonance imaging (MRI)[40,41] or endosonography[42-44] before and after infliximab treatment and traces of inflammation in fistula tracts exist even after repeated doses of infliximab for a long period of time (54 weeks).

Furthermore, it seems that all kinds of fistulae do not heal with the same rate. In the study of Present *et al*[36] only patients with external fistulae participated. A recent study examined the differences in response to infliximab among patients with different types of fistulae (external, internal or mixed).[45] Of the 60 patients who participated, 69% (24/35) of those in the external fistula group showed complete response to infliximab treatment vs 13% (2/16) in the internal fistula group and 10% (1/9) in the mixed fistula group. Based on these results it could be suggested that external fistulae have a higher rate of complete response to infliximab compared to internal fistulae.

A very important issue seems to be the adverse events observed in patients treated with infliximab. These include infusion reactions, delayed hypersensitivity reactions, increased overall rate of infections (including pneumonia, sepsis, tuberculosis, histoplasmosis, coccidioidomycosis, listeriosis, *Pneumonocystis Carinii* pneumonia and aspergillosis), formation of human antichimeric antibodies (HACA), formation of nuclear and anti-double-stranded DNA antibodies, drug-induced lupus, demyelinating disorders, possible development of lymphomas or other kinds of malignancy and death in a reported rate of 1%.[46,47]

Based on these data the question of whether anti-TNF treatment could be a true alternative treatment option to surgical intervention has been raised. Since the results of surgical interventions vary depending on the

type of fistula, even among the perianal fistulae, a comparison of these interventions with anti-TNF treatment is almost impossible.

Many perianal fistulae in CD, especially when the rectum is not involved, are simple and superficial. Most of these fistulae can be cured definitely by fistulotomy with healing rates between 70 and 100%, low recurrence rates of < 20% and low risk for incontinence.[48,50] It could be suggested therefore, that in simple fistulae without rectal CD involvement, surgical treatment in combination with antibiotics is still the treatment of choice.

The therapeutic strategy is not so simple in the cases with complex fistulae. Firstly, complex fistulae should be examined both by MRI and under anesthesia (EUA) in order to define disease extent and to identify abscesses that require underoofing and drainage. In these patients surgical fistulotomy may be associated with significant morbidity.[51,52] However, it is generally advised that surgical treatment should be combined with medical treatment, whenever possible. A small recent study in 32 patients with perianal FCD has compared the efficacy of infliximab alone with infliximab as an adjunct to surgical EUA with seton placement.[53] Patients who had an EUA prior to infliximab infusions had a better initial response (100% vs. 82.6%, $p=0.014$), lower recurrence rate (44% vs. 79%, $p=0.001$), and longer time to recurrence (13.5 months vs. 3.6 months, $p=0.0001$) compared with patients receiving infliximab alone. Additionally, findings from a small retrospective case series in which a single center experience of 29 patients was reviewed, support the notion that combination of seton placement, infliximab infusion and immunosuppression is beneficial in complicated and rectovaginal fistulae.[54]

In another retrospective study, the question of what proportion of patients treated with infliximab eventually undergo surgery was addressed.[55] It was found that 6/26 patients had complete fistula closure, 12/26 had a partial response to infliximab and 14/26 still required surgery (10 bowel resection, 4 perianal procedures); however an additional 6 patients with persisting draining fistulae declined surgery.

Towards the aim of reducing the number of patients requiring surgery after infliximab infusion fails to close fistulae, various combinations of complementary agents alone or together with infliximab have been tested. Such studies include tacrolimus in cases of FCD, which is refractory to conventional therapy including infliximab,[56] combination of infliximab with azathioprine[57] or methotrexate[58] as maintenance treatment and combination of infliximab infusion with ciprofloxacin.[59] Specifically, the combination of infliximab with immunosuppressives includes some advantages such as decreased rate of adverse reactions related to antibody formation to infliximab, the preservation of drug efficacy and even increased and more prolonged response rates.[60].

Furthermore in a recent pilot study, the feasibility and safety of local injection of infliximab in selected patients with severe perianal CD, either refractory or contradicted to systemic infliximab infusion was investigated.[61] The injection of 15 to 21 mg of infliximab, in association with surgical treatment, was performed at the internal and external orifices and along the fistula tract. The treatment was repeated for at least six times. Ten of 15 patients healed after 3 to 12 infusions and no major adverse effects were reported.

Finally, a possible role for infliximab in the perioperative period remains anecdotal, but is currently under evaluation. Some authors suggest that complex perianal fistulae should be managed with infliximab prior to surgery. This may be sound logic if definitive surgical procedures, including fistulectomy, fistulotomy or an advancement flap are being considered, as it is generally advised that such procedures should not be attempted until sepsis has been adequately treated. Infliximab should not be used to defer surgical drainage of perianal sepsis.

CONCLUSIONS

Infliximab is the only medical therapy that has been shown to be effective for the treatment of FCD. Although infliximab is a useful adjunct in the management of selected patients, the cornerstones of management of FCD remain rather unchanged. Current evidence suggests that its use should be restricted to those in whom optimal medical and surgical first and second line therapy has failed. In those patients with FCD, where infliximab therapy is chosen, regular maintenance therapy with infliximab is likely to be required. Although safe and generally well tolerated, the drug carries side effects that clinicians need to be able to recognize and to manage properly. Future prospective trials on medical therapy and the combination of medical and surgical therapy for complex fistulae and internal fistulae are needed in order to define the potential and the limitations of these novel therapeutic approaches such as infliximab.

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