# Combined Approach with Infliximab, Surgery, and Methotrexate in Severe Fistulizing Anoperineal Crohn's Disease: Results from a Prospective Study

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**Background:** Infliximab is the only medical therapy that has been proven to be effective in fistulizing Crohn's disease (CD), but the recurrence rate of fistulas is high despite maintenance therapy. The aim of this prospective study was to evaluate the short- and long-term efficacy of a combined schedule with infliximab, methotrexate, and sphincter-sparing surgery in patients with severe fistulizing anoperineal CD.

**Methods:** From January 2006 to November 2007, all consecutive patients in three referral centers with severe fistulizing anoperineal CD were prospectively included after primary drainage. At inclusion, patients received three infliximab infusions at weeks 0, 2, and 6, and maintenance therapy with methotrexate. A second optimized surgical step consisting of at least removal of setons was performed between the second and the third infliximab infusions.

**Results:** Thirty-four CD patients (26 women; median age 38.5 years) with complex anoperineal fistula were enrolled (including 9 with recto-vaginal fistulas, and 10 with anorectal stenosis). At week 14 the response rate was 85% with 74% complete responders. At 1 year, 50% were still responders; luminal CD worsening was the major cause of relapse. Median Perineal Disease Activity Index (PDAI) and magnetic resonance imaging (MRI) scores significantly decreased from baseline to week 50.

**Conclusions:** A combined approach with infliximab induction, two surgical sphincter-sparing steps and methotrexate is effective in achieving short-term response in severe fistulizing anoperineal CD. The best maintenance regimen remains to be determined.

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**Key Words:** Crohn's disease, infliximab, methotrexate, perineal fistula

Fistulizing anoperineal Crohn's disease (CD) complicates primary lesions such as fissures or ulcers. It occurs in 23%–26% of patients with CD after 20 years of evolution and associated rectal lesions observed in 92% of patients represent the main risk factor.[1–3] Fistulizing anoperineal CD is a very disabling condition due to sphincter and perineal tissue destruction leading to surgery (with diverting stomy in 6% of cases[4]) and psychosocial complications.[5]

Because of a lack of controlled trials, the management of CD patients with complex anoperineal fistula is not standardized. Both surgical and medical approaches should be considered. According to the European Crohn's Colitis Organisation (ECCO) statements, surgical drainage, antibiotics, or thiopurine therapy are the first choices, and infliximab is a second-line therapy. However, sequence and timing of each treatment are not clearly defined.[6] Proctological surgery is a crucial issue, consisting of at least primary drainage with noncutting setons.[1,7] Antibiotics have little efficacy, and fistulas frequently relapse with treatment withdrawal.[8] Data from controlled trials of azathioprine are scarce and not convincing.[9–11] Methotrexate has been poorly investigated in this setting and only small open-label series after azathioprine intolerance or failure have been reported so far.[12,13] Infliximab has demonstrated its efficacy in fistulizing CD.[14,15] However, only 36% of patients were still responders at 1 year despite maintenance therapy with infliximab in the per-protocol analysis of the ACCENT II study.[15] It has been suggested that remaining fistula tracks on magnetic resonance imaging (MRI) examination may favor fistula recurrence in responders.[16] Furthermore, although there has not been a controlled trial of adalimumab specifically in patients with fistula, subanalysis

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of the CHARM study and its open-label extension suggested a sustained efficacy.[17]

These treatments have been evaluated independently and little is known about a multimodal approach combining anti-TNF agents, immunosuppressants, and proctological surgery. Some studies have suggested that infliximab efficacy could be improved by methotrexate and/or selective seton drainage.[18,19] Therefore, the aim of this study was to evaluate in an open prospective manner the short- and long-term efficacy of a strategy combining induction with infliximab and sphincter-sparing surgery and maintenance therapy with methotrexate in patients with severe fistulizing anoperineal CD.

## PATIENTS AND METHODS

### Selection of Patients and Study Schedule

From January 2006 to November 2007, all consecutive patients with fistulizing anoperineal CD referred in three gastroenterology departments in the Bordeaux area (Hôpital Haut-Lévêque, Hôpital Saint-André, MSP Bagatelle) were prospectively included in an open study. Eligible patients were adults (age 18 years or more) with complex anoperineal fistulizing CD according to usual criteria[1] including recto-vaginal tracks. A primary drainage with noncutting seton(s) was performed before starting infliximab except in two cases with short fistula track and complete drainage as judged by the surgeon. Antibiotics could be added at this stage.

If given, salicylates and steroids were at stable doses before inclusion within the last 2 and 3 weeks, respectively; azathioprine was discontinued at the time of primary drainage. The following criteria led to exclusion: contraindication to infliximab and/or methotrexate, prior treatment with infliximab or methotrexate within the last 8 weeks, nondrained abscess on MRI, other types of fistula including enterocutaneous fistula without coexisting perineal fistula, intestinal or anoperineal (except primary drainage) surgery within the last 3 months, or ostomy.

The study schedule is summarized in Figure 1. Within 2–3 months following primary drainage of the perineal fistula, patients started methotrexate (25 mg weekly by subcutaneous or intramuscular route, followed by 5 mg of folic acid the following day). One week after starting methotrexate, an infliximab induction schedule was administered with three 5 mg/kg infusions at weeks 0, 2, and 6. If given at baseline, steroids were tapered since starting infliximab and stopped before week 6. Inclusion date was defined at time of the first infliximab infusion. Four experienced proctology surgeons (D.B., F.P., A.C., and F.J.) were involved in the study. The second surgical procedure was performed between the second and the third infliximab infusions. All setons were removed at this time. As judged by the surgeon, sphincter-sparing reconstructive surgery was considered at that time. Antibiotics, cyclosporine, FK506, other anti-TNF therapy, thalidomide, and artificial nutrition were not given during the study.

Visits including physical examination and routine laboratory analyses were planned at weeks 0, 2, 4, 6, 10, 14, and then every 8 weeks until loss of response. Safety was ascertained at each visit. Liver fibrosis was assessed at baseline and then yearly with noninvasive methods such as FibroScan and FibroTest as previously described.[20]

Evaluation of fistulizing CD was performed with the Perineal Disease Activity Index (PDAI) and pelvic MRI according to the Van Assche classification[16] after drainage and before inclusion, and at weeks 14 and 50. PDAI is a functional score, ranging from 0 (no symptoms) to 20, including discharge, pain, restriction of sexual activity, type of perineal disease, and degree of induration. The Van Assche MRI score, ranging from 0 (normal) to 22 (severe disease) evaluates both criteria of local extension of fistula, relation to the anal sphincters, and active local inflammation.

MRI examination was performed using a 1.5T MR imager (Sonata, Siemens, Germany) using a dedicated phased array coil. Scanning protocol included axial enhanced T1 2D-gradient-echo sequences (in phase and opposed phase), axial T2-weighted HASTE sequence, and axial T2-weighted turbo-spin echo sequence with fat saturation. Patients received a standard intravenous bolus (0.2 mL/kg) of gadolinium-chelate contrast agent (Dotarem, Guerbet, or Magnevist, Schering) delivered at an injection rate of 2 mL/kg with a flush of 20 mL of 0.9% saline solution. Early T1-weighted VIBE sequences were performed at 15, 60, and 110 seconds after injection.

### Definition of Response

Short-term clinical response was assessed 14 weeks after the first infliximab infusion according to the Present criteria: fistula was considered to be closed when it no longer drained despite gentle finger compression.[14] The closure of all draining fistulas was considered as complete response and a reduction of at least 50% of draining fistula as partial response.

Primary response was defined at week 14 as complete or partial fistula response together with clinical remission off steroids of luminal CD assessed by the Crohn's Disease Activity Index (CDAI) $<150$.

Loss of response was defined by the recrudescence of draining fistulas, the need for a change in medication for CD, the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for CD, the discontinuation of methotrexate, or loss to follow-up.

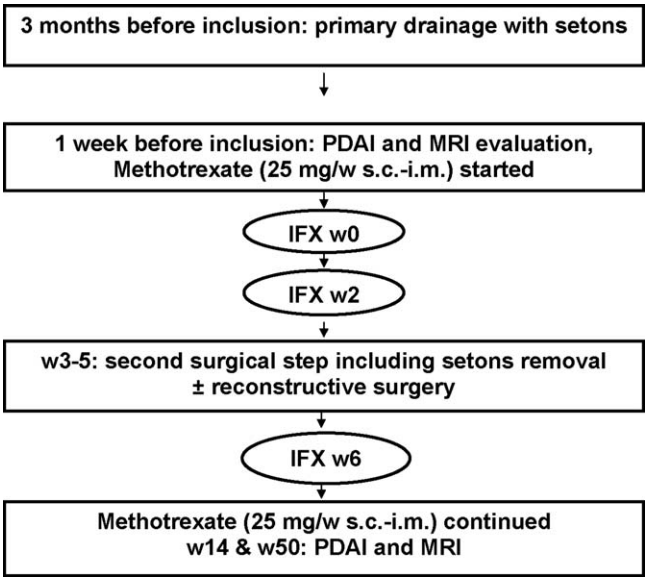


**FIGURE 1.** Study schedule (w: week; s.c.: subcutaneous; i.m.: intramuscular).

### Outcomes

Analysis was performed on an intention-to-treat basis. The primary endpoint was the primary response rate at week 14. Secondary endpoints were: 1) time to loss of response for primary responders; 2) time to fistula reopening for primary responders; 3) PDAI, and van Assche MRI score at weeks 0, 14, and 50; and 4) safety.

### Ethical Considerations

All patients received treatment because of the clinical need. Treatment was open and unblinded. Drugs used were those normally employed in CD, according to licensed or published doses and frequency. All patients were treated only after full and informed consent.

### Statistical Analysis

Descriptive values are expressed as percentages and median (range). Comparisons of quantitative data were made using the nonparametric Wilcoxon rank-sum test. Qualitative data were analyzed using the chi-square test or Fisher's exact test when appropriate. The remission rates in relation to time were estimated by the Kaplan–Meier method followed by testing the log-rank for comparison of remission curves. To assess the association between the response at week 14 and the different variables logistic regression was used. The difference was statistically significant at $P < 0.05$. Statistics were performed with SPSS 9.0 (Chicago, IL).

## RESULTS

### Characteristics of the Patients

Thirty-four patients were included in the study: 26 (76%) were women; median age was 38.5 years (range: 23–68). Their main characteristics at baseline are reported in Table 1. The median duration of disease before inclusion was 7 years (range: 0–25); disease location was ileal in 1 patient (3%), colonic in 13 patients (38%), and ileocolonic in 18 patients (53%). Twenty-eight patients (82%) were previously treated with corticosteroids, 21 (62%) with azathioprine, 7 (21%) with methotrexate, and 9 (26%) with infliximab. Fifteen patients (44%) had already undergone intestinal resection. At inclusion, almost half of the patients had an active luminal disease (53% of patients with CDAI >150) and 38% had a C-reactive protein (CRP) >20 mg/L.

Concerning fistulizing anoperineal CD, 23 patients (68%) had previously undergone perineal surgery. Details of baseline fistula characteristics are presented in Table 2.

**TABLE 1.** Main Characteristics at Baseline of the 34 Included Patients

| | *n*=34 |
|---|---|
| Median age, years [range] | 38.5 [23-68] |
| Female gender, *n* (%) | 26 (76) |
| Median disease duration, years [range] | 7 [0-25] |
| Age at diagnosis,* *n* (%) | |
| Below 16 (A1) | 1 (3) |
| Between 17 and 40 (A2) | 27 (79) |
| Above 40 (A3) | 6 (18) |
| Disease location,* *n* (%) | |
| Ileal (L1) | 1 (3) |
| Colonic (L2) | 13 (38) |
| Ileocolonic (L3) | 18 (53) |
| Upper GI tract (L4) + L1 or L2 or L3 | 3 (9) |
| Ano-perineal disease alone | 2 (6) |
| Disease behavior,* *n* (%) | |
| Nonstructuring nonpenetrating (B1) | 21 (62) |
| Stricturing (B2) | 6 (18) |
| Penetrating (B3) | 7 (21) |
| Current smokers, *n* (%) | 15 (44) |
| Previous intestinal resection, *n* (%) | 15 (44) |
| Previous treatments, *n* (%) | |
| Corticosteroids | 28 (82) |
| AZA/6-MP | 21 (62) |
| Methotrexate | 7 (21) |
| Infliximab | 9 (26) |
| CDAI > 150 at inclusion | 18 (53) |
| CRP level ≥ 20 mg/L, *n* (%) | 13 (38) |

*Age at diagnosis, Crohn's disease location, and behavior according to the Montreal Classification.[38] AZA/6-MP: azathioprine/6-mercaptopurine.

**TABLE 2.** Ano-perineal Disease Characteristics at Baseline of the 34 Included Patients

| | | *n*=34 |
|---|---|---|
| Previous perineal surgery,* *n* (%) | None | 11 (32) |
| | 1 surgery | 14 (41) |
| | 2 or more | 9 (26) |
| Parks classification, *n* (%) | Intersphincteric | 1 (3) |
| | Transsphincteric | 18 (53) |
| | Suprashincteric | 4 (12) |
| | Extrasphincteric | 11 (32) |
| Ano/recto-vaginal fistula, *n* (%) | | 9 (26) |
| Ano-rectal stenosis, *n* (%) | | 10 (29) |
| Number of external orifices, *n* (%) | None (intramural fistulas) | 2 (6) |
| | One | 20 (59) |
| | Two or more | 12 (35) |
| Median PDAI score, [range] | | 11 [8-13] |
| Median MRI Van Assche score, [range] | | 15 [12-19] |

*Excluding the primary drainage.

All but one patient had at least one complex fistula at inclusion. One patient (3%) had an intersphincteric track considered as complex fistula as it was the fourth surgical procedure. Twelve patients (35%) had two or more external orifices. Nine patients (26%) had recto- or ano-vaginal fistula, and 10 patients (29%) had an associated anorectal stenosis.

## Second Surgical Procedure

The median time between the first infliximab infusion and the second surgical procedure was 31 days (range: 20–55). Reconstructive procedure was not considered in the five patients with active proctitis at this time. Details of the second surgical step are given in Table 3. In 11 patients (32%), the second surgical step was a simple approach: removal of setons alone in seven patients, and associated with fistolotomy in four patients. Ten patients (29%) had fibrin glue applied in the fistula track. In the 13 (38%) remaining patients a reconstructive procedure was performed: 11 had a flap advancement procedure (associated in two patients with fibrin glue application) and two had recto-vaginal fistula repair with Musset perineotomy.

## Response to the Induction Regimen

At week 14 the primary objective of the study was achieved in 29 patients (85%). A complete fistula response was obtained in 25 patients (74%). No predictive factor, such as clinical activity at baseline or prior infliximab treatment, was associated with primary response at week 14. In the five nonresponders at week 14, three had rectal or anal stenosis at baseline and three had rectal- or ano-vaginal fistula (associated in one case with stenosis). Two of these patients had a diverting stoma during follow-up.

**TABLE 3.** Second Surgical Step Procedures Performed Between the Second and the Third Infliximab Infusions

| Technique | *n* (%) |
|---|---|
| Setons removal* | 32 (100) |
| Simple approach | 11 (32) |
| Seton removal alone | 7 (21) |
| Fistulotomy | 4 (12) |
| Fibrin glue | 10 (29) |
| Reconstructive surgery | 13 (38) |
| Flap | 9 (26) |
| Flap + glue | 2 (6) |
| Recto-vaginal fistula repair | 2 (6) |

*Two patients without seton at baseline.

## Secondary Endpoints

The median time to loss of response among primary responders was 57 weeks. In the intention-to-treat analysis, the 50-week actuarial survival without loss of response and without perineal relapse was 50%. Kaplan–Meier curves of global and anoperineal survival without relapse in primary responders are shown in Figure 2. Eighteen months after inclusion, the global and perineal response rates were 34% and 84%, respectively. The most common criterion met for

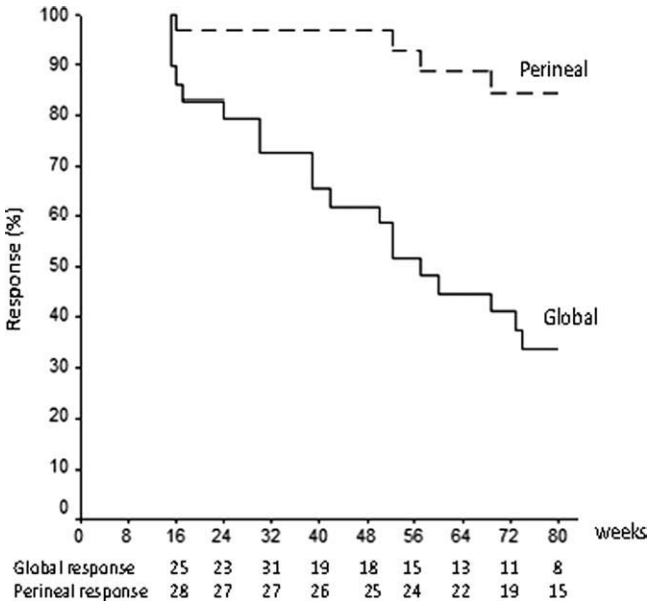


**FIGURE 2.** Time to loss of global and perineal response among responders at week 14 (Kaplan–Meier curve).

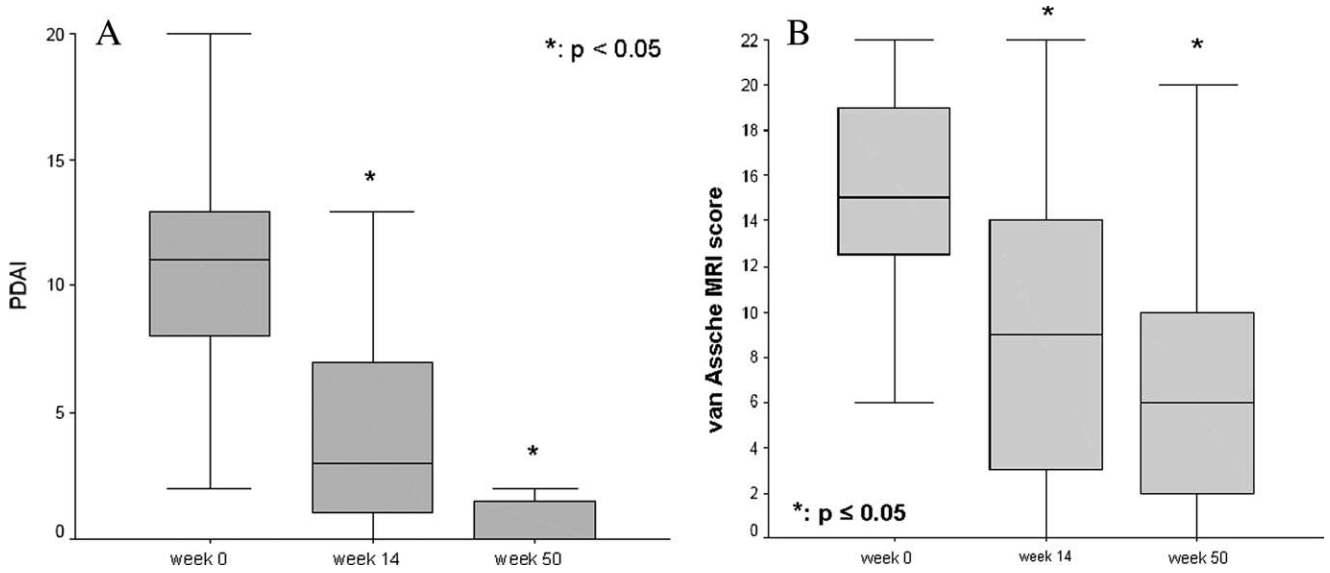


**FIGURE 3.** Evolution of Perineal Disease Activity Index score from baseline to week 50 (minimum, maximum, interquartile range, and median) (A). Evolution of van Assche MRI score from baseline to week 50 (minimum, maximum, interquartile range, and median) (B).

the loss of response after primary response was the relapse of luminal CD ($n = 11/29$ patients at week 80, 38%). A minority of primary responders (3/29, 10%) experienced anoperineal relapse during the follow-up. Three patients (10%) were considered as having had loss of response because of methotrexate withdrawal, despite luminal and anoperineal response. Two patients (7%) were lost during the follow-up at weeks 52 and 57, and were still responders at their last visits. Due to the small number of events, the median time to loss of perineal response was not assessable.

In the subgroup of patients with recto-vaginal fistula at baseline, 6/9 (66%) were responders at week 14. The second surgical procedure was simple seton removal in two patients, rectal flap advancement procedure in five patients—including one associated with fibrin glue application—and recto-vaginal fistula repair with Musset perineotomy in two patients. None had fistulotomy or fibrin glue application alone. None of the six primary responders reopened their recto-vaginal fistula tracks during follow-up. Luminal CD relapse occurred in three patients before week 50. Overall, 3/9 (33%) had a sustained perineal and luminal response at week 50.

Median PDAI at weeks 0, 14, and 50 decreased significantly from 11, to 3 and 0, respectively ($P < 0.001$ between weeks 0 and 14, $P < 0.001$ between weeks 0 and 50, $P = 0.04$ between weeks 14 and 50; Fig. 3A). The same trend was observed with the median van Assche MRI score decreasing from 15 at week 0, to 9 and 4 at weeks 14 and 50, respectively ($P < 0.001$ between week 0 and 14, $P < 0.001$ between week 0 and 50, $P = 0.022$ between week 14 and 50; Fig. 3B). Fistula tracks completely healed in 6/17 (35%) patients on MRI evaluation at week 50 (Fig. 4).

### Safety

Adverse events occurred in 25 patients (74%). In 16 patients, side effects were mild and related to methotrexate (influenza-like illness and nausea, alopecia), leading to discontinuation of the drug in 5 (15%) cases. The median duration of treatment before withdrawal among these patients was 60 weeks. In four patients (12%) the side-effect was mild and transient alanine aminotransferase (ALT) increase. No case of significant liver fibrosis was identified at baseline and during follow-up according to FibroScan and FibroTest measurements. In five patients (15%) the side effect was severe infection during the infliximab induction: two pyelonephritis, two cholecystitis, and one cytomegalovirus (CMV) hepatitis. Hypersensitivity reactions to infliximab occurred in two patients (one acute and one delayed). No death was observed.

## DISCUSSION

Because of the variety of clinical presentations and the lack of guidelines, the management of fistulizing anoperineal CD is a difficult challenge in clinical practice. The recommendations from the ECCO group are mostly based on expert opinion (grade D) except for infliximab efficacy.[6] However, the relapse rate despite maintenance therapy with infliximab is high and there is a need for more effective long-term strategies. In this study performed in patients with complex anoperineal fistula, combining infliximab induction with methotrexate and a two-step conservative

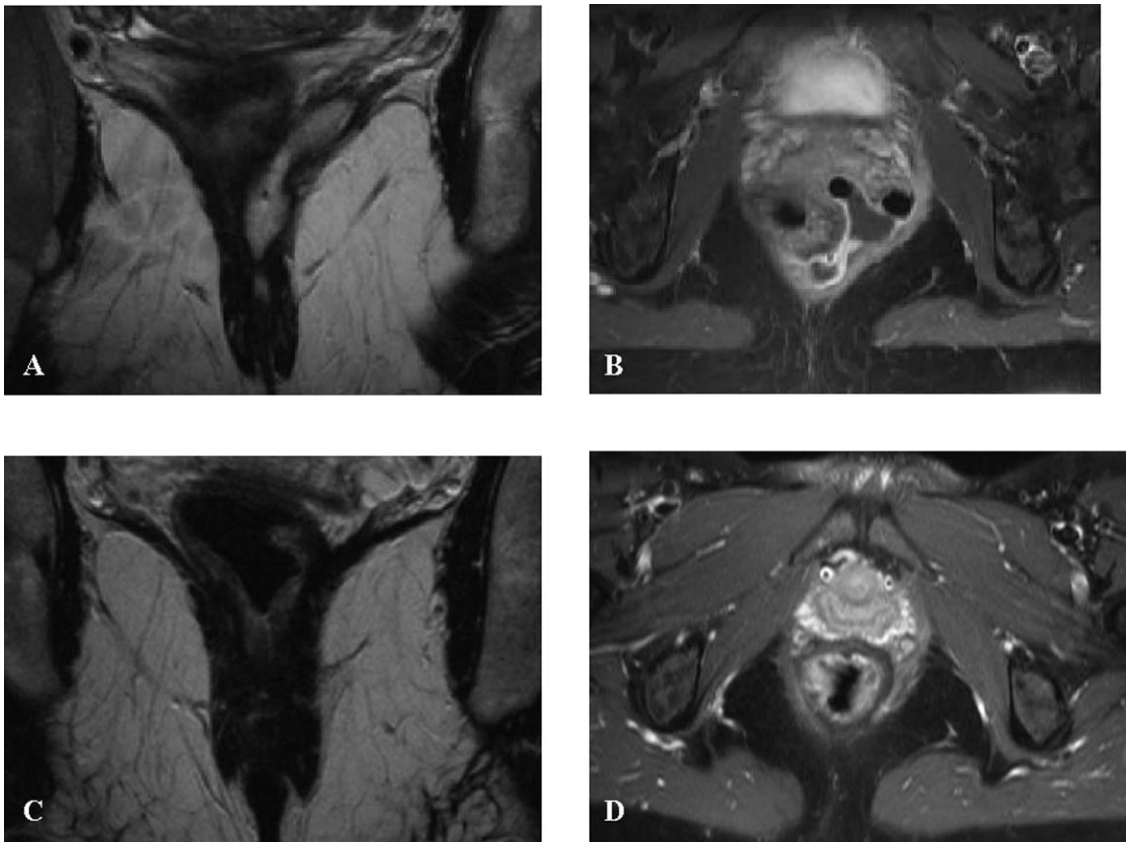


**FIGURE 4.** Pelvic MRI scan of a 41-year-woman with a pure anoperineal CD. On coronal T2 MRI at baseline (A), the supra-sphincteric fistula track extended to a supralevator collection was hyperintense and enhanced on axial T1 after gadolinium injection showing a horseshoe extension and a marked thickening of the rectal wall (B). At week 50, after a second surgical reconstructive surgery associating flap with fibrin glue application, the patient had a complete clinical response with disappearance of hyperintensity on T2 (C), and of enhancement after gadolinium injection on T1 associated with persisting mild thickening rectal wall (D).

surgical approach, a 74% short-term (14 weeks) complete response rate was achieved. Considering long-term results, this multimodal approach allowed a prolonged (18 months) perineal response in 84% of patients. By contrast, this strategy failed to achieve a prolonged remission of luminal disease in the majority of patients.

The treatment of both luminal and anoperineal diseases should be optimized when dealing with fistulizing CD. This is clearly demonstrated by the results of the ACCENT II trial in which among the 42% of patients who experienced a loss of response while on infliximab maintenance therapy, 25% needed a change in the treatment of CD while 16% experienced a recrudescence of fistulas.[15] As shown in MRI studies, the persistence of the fistula track while the external orifice is closed and fistula appears healed suggests drying up but not complete healing.[16,21,22] This was further confirmed by a recent prospective study in 19 patients where infliximab therapy was driven according to fistula MRI healing.[23] Therefore, the rectal mucosal healing achieved with infliximab in fistulizing anoperineal CD could be the main reason explaining its efficacy. Combining medical treatments with sphincter-sparing surgery is an attractive approach in order to heal the fistula track, remove setons, and control luminal inflammation. In a small prospective study, a multistep strategy (including three infliximab infusions in case of active proctitis, 3 months after placement of setons) achieved a response rate exceeding 97% after 1 year in 17 highly selected patients.[24]

The standardized multimodal approach described here combining infliximab therapy with a surgical procedure allowed a 74% complete response rate which favorably compares with the 48% response rate obtained in the ACCENT II trial.[15] These quite satisfactory results were obtained despite inclusion of more severe patients, i.e., with anorectal stricture or with recto-vaginal fistula tracks. Although the series reported here involved a modest number of patients, this result supports the concept of a two-step surgical approach. First, the abscess on peri-anal fistula requires an urgent sphincter-sparing drainage, most

often using noncutting setons.[16] Then, long-term drainage with unfastened setons could be considered; however, it is poorly accepted by patients, exposes to recurrence,[25,26] and does not allow fistula healing. A simple removal of setons, which is more comfortable for patients, also exposes to recurrence in 30%–50% of cases.[27] Therefore, a second surgical step should be considered after primary drainage. The precondition for this surgery is the control of the luminal CD, especially in the rectum and this further justifies the need for an effective medical therapy with infliximab. For the time being, recommendations about the surgical procedures mandatory to obtain a fistula healing in peri-anal CD are elusive,[6] but several types of procedures can be performed. Fistulotomy may be used on very low fistulas. Covering the primary orifice and/or obstructing the fistula track represent interesting approaches recently highlighted in a randomized controlled study showing that fibrin glue application provides more short-term responders than a sham procedure. However, in the subgroup of patients with a complex fistula at baseline, the response rate with fibrin-glue was low (25%) and not different than in controls.[7] Plugs have to be adequately evaluated in this setting. Endo-rectal advancement flaps can be also considered in complex fistulas, with interesting results in small series including highly selected patients.[1] In the current study the main second surgical procedures consisted of simple seton removal, fibrin glue application alone, and flap advancement. The choice of the procedure relied mainly on the type and localization of the fistula, the presence of inflamed rectal mucosa, and the personal experience of the surgeon. The type of surgery performed at this time was not a predictive factor of response at week 14. However, considering the number of patients included, it is difficult to draw any definite conclusion about the best surgical approach.

There are no recommendations about the best drainage duration with setons. Moreover, when combining infliximab with perineal surgery, little is known about the ideal surgical time after starting the biologic therapy, although it is reported to range from 3 weeks to 3 months in retrospective studies. According to previous studies and the time to heal the rectal mucosa, time to the surgical procedure for setons removal was standardized here to between the second and the third infliximab infusion.[18,23,24,28,29] The results suggest that this second surgical step is safe and effective when performed 1 month after starting infliximab therapy.

The issue of recto-vaginal fistula is particularly demonstrative of the efficacy of a combined approach. Recto-vaginal fistula has an ≈3%–5% incidence in women with CD. It is a debilitating complication with very poor prognosis, as observed when compared to other fistula locations.[30,31] The open-label induction with three infliximab infusions in the ACCENT II study provided 45% of closure at week 14 of the 29 recto-vaginal fistulas treated.[31] The combined approach proposed in the current study provided 66% recto-vaginal fistula closure without any relapse at 1 year. The reconstructive surgical procedure performed in 7/9 patients (rectal flap advancement procedure or recto-vaginal fistula repair via Musset perineotomy) may explain this higher response rate. Furthermore, comparison must be interpreted with caution because of the small sample size and the different definition of closure based only on anatomic response in this study.

If the combined approach reported here proved to be very effective in achieving a short-term (week 14) complete response, the overall long-term results are far from satisfactory since only 34% of the patients had a sustained (18 months) response rate. However, it is of note that most failures were related to recurrence of the luminal disease while 84% of the short-term responders still had fistula closure after an 80-week follow-up. The decrease of van Assche score illustrates only the improvement of the fistulizing disease and suggests a deep remission with fistula healing. The dissociated evolution between luminal and anoperineal CDs further supports the efficacy of the initial combined therapy on fistulas which was sustained despite the lack of efficacy of methotrexate to achieve long-term luminal remission. Indeed, one can hardly consider that methotrexate was effective to control anoperineal disease but not luminal disease.

When considering luminal CD, methotrexate, which is usually proposed after azathioprine failure or intolerance, has been shown to have a steroid-sparing effect[32] and, although the duration of treatment is not clearly defined, this compound could provide prolonged remission.[33,34] Results presented here are in accordance with data reported by others in both uncontrolled and placebo-controlled studies in luminal CD, showing an increasing proportion of patients becoming methotrexate-refractory with time. However, this is the first prospective study assessing prospectively the 2-year remission rate with this drug in CD. The induction schedule used may have provided better long-term results for luminal disease with infliximab as maintenance therapy. Indeed, as with azathioprine, methotrexate reduces anti-infliximab antibody formation which leads to loss of efficacy or intolerance in case of additional infliximab infusions,[35] which led us to consider an infliximab induction regimen associated with long-term methotrexate treatment. Such a combined approach has also given good results in patients with luminal CD receiving maintenance therapy with azathioprine.[36,37]

In conclusion, the study reported here shows that combining surgery, infliximab, and methotrexate provides both short-term and sustained responses in fistulizing anoperineal CD. In accordance with the improvement found by

MRI examination, few patients experienced fistula relapse after primary closure, suggesting that a highly effective initial treatment that aims at healing the fistula track is followed by limited loss of response. This combined approach should be further evaluated in larger multicenter studies. However, since most patients experienced luminal relapse during the follow-up while on maintenance therapy with methotrexate, the best maintenance therapy needs to be further determined.

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