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Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure

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Abstract

Background: Infliximab has improved the management of perianal Crohn's disease, but intolerance and loss of efficacy can occur. The use of a second antibody can be less effective.
Objective: Our aim was to determine if the use of adalimumab, based on a multidisciplinary strategy, can enhance outcomes for patients with fistulizing disease and infliximab failure.
Material and methods: Sixteen patients with perianal disease and infliximab failure were treated with adalimumab. Complex fistulas were assessed using magnetic resonance imaging (MRI). Patients with severe conditions as determined by radiology were examined under anesthesia, and seton placement was performed when appropriate. Setons were removed when external discharge had ceased and there was no radiological evidence of fistula activity.
Results: Nine patients (56%) underwent MRI. Setons were inserted in seven (43%). The baseline perianal disease activity index (PDAI) decreased after 4 weeks and remained at similar levels 24 and 48 weeks after treatment. The complete response rate was 50% after four weeks and 87.5% of these patients remained in remission after 48 weeks of treatment.
Conclusions: For patients with Crohn's perianal fistulas and infliximab failure, adalimumab as a multidisciplinary approach to management, using MRI to guide surgical drainage when necessary, results in a favourable response and low recurrence rate.

Abbreviations: CR, Complete response; PR, Partial response; MRI, Magnetic resonance imaging; PDAI, Perianal disease activity index; CD, Crohn's disease; EUS, Endosonography; EUA, Exploration under anaesthesia; CDAI, Crohn's disease activity index.

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1. Introduction

Perianal fistulas affect 14%–38% of patients with Crohn's disease (CD) and often require surgical treatment because of their frequent recurrence and complexity.[1] Antibiotics and immunosuppressant agents have been used for treatment, although their efficacy for the sustained closure of fistulas has not been proved.[2,3]

The introduction of anti-TNFα monoclonal antibodies has improved the prognosis of Crohn's perianal fistulas.[4] The results of the multicenter infliximab maintenance study ACCENT II revealed a 63% response to initial infusion, but maintenance of complete fistula closure occurred in only 36% of patients.[5] Several studies using magnetic resonance imaging (MRI) and anal endosonography (EUS) have shown persistent fistula activity after infliximab treatment even after the fistula stops draining.[6–8] However, it has been suggested that this residual inflammatory activity may cause recurrent fistulas and new abscesses.

The best outcomes have been achieved when surgical and medical therapies have been used in conjunction. The insertion of draining setons along fistula trajectories prior to the institution of infliximab therapy improves early and long-term remission rates.[8–10]

The first studies on adalimumab treatment of fistulizing disease patients who experienced intolerance or loss of infliximab efficacy found that complete remission occurred in 23%–33%.[11–13] In the CHARM study,[14] fistulizing disease patients treated with adalimumab had a 35% complete remission rate in the short- and long-term (26 and 56 weeks). Complete fistula healing was sustained for up to 2 years by most patients in an open-label extension trial.[15]

Prolonged treatment with infliximab can decrease its efficacy and cause allergic reactions associated with anti-infliximab antibodies.[16] In all these cases adalimumab treatment can be an option. The aim of our study is to determine if the use of MRI to initially assess complex fistulas, as well as guiding seton drainage, can improve the rate of durable fistula healing in this difficult-to-treat Crohn's disease patient population.

2. Material and methods

2.1. Patient selection

Patients with active, draining perianal Crohn's fistulas who had experienced a decrease in the efficacy of infliximab, or had developed intolerance, were included in the study. All patients had one or more episodes of draining perianal fistulas at the time of inclusion as a complication of CD that was confirmed by endoscopy or pathological examination.

Concurrent therapies for CD, including fixed dose of aminosalicylates, azathioprine, and antibiotics were permitted. Changes in the doses of medications were recorded.

Loss of efficacy was defined as the development of abscesses or relapse of discharge through existing or new fistula orifices. Intolerance was defined as the development of a clinically significant acute or late infusion reaction requiring suspension of infliximab treatment. Acute reactions present during the first 24 h of infliximab infusion and manifest as fever, chills, skin rash, urticaria, angioedema, breathing difficulties or hypotension. Late reactions occur 24 h to 15 days after infliximab infusion and are characterized by myalgia, joint pain, fever, or rash.

2.2. Study design

A multicenter, prospective, observational study was conducted by the Inflammatory Bowel Units of four tertiary Hospitals in Galicia. This was a consecutive case series that included all patients referred with active fistulizing Crohn's disease and loss of efficacy/intolerance of infliximab, during the period 2006–2008. This work has been approved by the appropriate ethical committees.

Baseline demographic details and perianal fistula characteristics were recorded (Tables 1 and 2). Patients were examined clinically for the number of external openings, actively draining fistula and the presence of active rectal disease on sigmoidoscopy at the start of the study.

A classification of the patients, on the basis of the type of fistula present, was performed. A simple fistula is a superficial, inter-sphincteric or low trans-sphincteric fistula with only one opening, and is not associated with an abscess and does not connect to an adjacent structure. In this group, we must differentiate between those without and with proctitis. A complex fistula is one that involves more of the anal sphincters, has multiple openings, is associated with a perianal abscess and/or connects to an adjacent structure.

Regarding these definitions, the cases included in this study corresponded to complex fistules, and simple fistulas with proctitis, both considered difficult-to-treat fistules.[17]

Magnetic resonance imaging (MRI) was performed on patients with complex fistules. MRI scan was performed with a Philips Gyroscan 1.0 T (Gyroscan Philips Holland), using standard T2 sagittal sequences. High resolution axial and coronal T2 sequences with fat saturation in the plane of the anal canal were obtained.

If MRI showed the presence of a severe disease,[6] exploration under anesthesia (EUA) was carried out by a colorectal surgeon who was aware of the MRI findings.

Table 1 Demographic and clinical features of the study population.

Characteristics and parameters	N(%)	Mean ± SD
Male	10(62.5%)	-
Age (years)	16	33.9 ± 7.8
Age at diagnosis	16	24.4 ± 7.7
Smoking status		
Smoker	9(56%)	-
Non-smoker	7(44%)	
Location of disease		
Ileal	1(6.25%)	-
Ileocolic	6(37.5%)	
Colic	9(56.2%)	
Current treatment		
Azathioprine	12(75%)	-
Antibiotics at diagnosis	11(68.7%)	
Reason for discontinuing infliximab		
Intolerance	7(43.7%)	-
Loss of response	9(56.2%)	

Table 2 Perianal fistula characteristics.

Characteristics and parameters	N(%)	Mean ± SD
Total number of fistulas	31	
Number of fistulas at baseline		
1 fistula	8(50%)	
2 fistulas	4(25%)	
3 fistulas	2(12.5%)	
>3 fistulas	2(12.5%)	
Type of fistula		
Simple	7(44%)	
Complex	9(56%)	
Baseline PDAI [a]	16	12.12 ± 1.82
MRI	9(56%)	
Baseline MRI score	9	13.56 ± 4.28
Seton drainage	7(43%)	

[a] Perianal Crohn's Disease activity index.

Draining of abscesses, cleaning of fistula tracks, and placement of loose setons were done when necessary.

Patients with simple fistules and proctitis received adalimumab treatment directly. After the initial evaluation, induction treatment with adalimumab was started at a dose of 160 mg/s, followed 2 weeks later by 80 mg/s. Maintenance therapy was 40 mg/s every other week.[18] In case of the loss of response, a weekly dose was performed.

2.3. Clinical evaluation

The patients were evaluated 4, 24, and 48 weeks after starting adalimumab treatment. The Crohn's disease activity index (CDAI) was completed at each visit. For CDAI, a score of <150 is regarded as reflecting clinical remission.

The effect of the drug on fistulizing disease was assessed based on changes in the perianal disease activity index (PDAI) and fistula discharge. The PDAI[19] takes the following lesional and functional aspects of the disease into account: the amount and characteristics of the discharge, the type and number of fistulas and abscesses, pain, and changes in sexual activity.

Fistula output was assessed using previously established measurement criteria. An open fistula was characterized based on the discharge of purulent material when digital pressure was applied to the track of the fistula. A complete response (CR) was defined as the absence of discharge between two consecutive visits and a partial response (PR) was defined as either closure of >50% in the number of externally draining fistulas, or a marked reduction in drainage of all fistulas together, sustained for at least two consecutive visits. Recurrence was defined as a reopened external fistula track with active drainage.

2.4. Radiological and surgical evaluation

Complex fistulas were evaluated using MRI. Fistulas were assessed according to their anatomical proximity to the sphincters and their extent. We also evaluated the location, extension, and number of fistula trajectories, along with the signs of active inflammation (T2 hyperintensity, presence of abscesses, and rectal wall involvement) according to the Van Assche MRI score for fistulizing perianal disease.[6]

If MRI showed the presence of severe disease, exploration under anesthesia was carried out by a surgeon who drained the abscesses and inserted loose setons.

There was no correlation between clinical responses after treatment and radiological fistula responses[6-8]. We performed MRI when no external discharge was observed and evaluated responses at the second clinical evaluation (24 weeks). When the resolution of inflammatory activity had been confirmed by radiology and no spontaneous or pressure-induced external discharge was observed, setons were removed to facilitate healing of the trajectory.

2.5. Statistical analysis

The CDAI, PDAI and MRI results are expressed as mean ± SD. Successive scores were analyzed using the non-parametric Friedman and Wilcoxon tests, as suitable. Statistical analysis was performed using the SPSS package version 9 (SPSS, Chicago, IL). A *P* value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

Sixteen patients (mean age, 33.9 years; range, 26–41 years) with fistulizing perianal disease, were included in the study. None of the cases was lost during the follow-up, previously established in 48 weeks. There were 10 males (62.5%) and 56% of patients (n = 9) were smokers. The mean interval between diagnosis of the disease and enrolment in the study was 9.5 years (range, 5–14 years) and the location of the disease was mainly colic (L2, 56%) or ileocolic (L3, 32.7%). Only two of the patients had ever undergone perianal surgery, which included one previous seton placement and one who had undergone fistulotomy.

Twelve patients (75%) received azathioprine and 11 (68%) received antibiotics. Adalimumab treatment was administered because of a loss of response to infliximab in 56.4% of cases and because of intolerance to infliximab in 43.6% of cases.

MRI was performed on nine patients with complex fistulas (56%). Emergency local drainage was performed in one case involving a suprasphincteric fistula with the reappearance of a gluteus abscess. In 43% of cases (n = 7), exploration was continued under general anaesthesia, during which the abscessed areas were cleaned and draining setons were inserted through internal trajectories.

PDAI score decreased from 12.12 ± 1.82 at baseline to 5.68 ± 2.75 four weeks after commencing adalimumab treatment ($P<0.001$). The PDAI score remained significantly lower than baseline 24 and 48 weeks after commencing adalimumab treatment (6.46 ± 3.37 and 6.93 ± 3.57, respectively; $P<0.001$; Fig. 1).

For all patients, the mean CDAI reduced significantly from baseline 215 ± 28.2 to 164 ± 16.2 at 4 weeks ($P<0.05$). The CDAI index remained significantly lower than baseline at 24 and 48 weeks (142 ± 16 and 148 ± 12, respectively; $P<0.05$).

Four weeks after commencing subcutaneous adalimumab treatment, 50% of patients had a CR (no fistula discharge despite application of pressure). The CR rate after 24 and

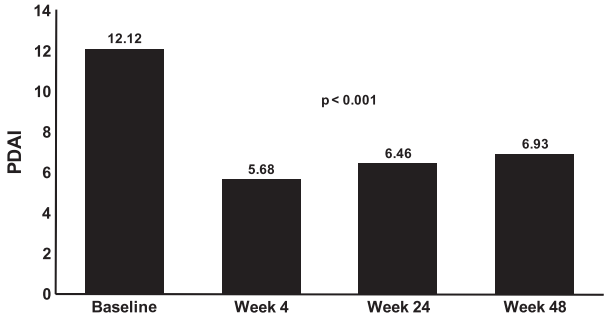

Figure 1 PDAI scores at baseline and after 4, 24, and 48 weeks of adalimumab treatment.

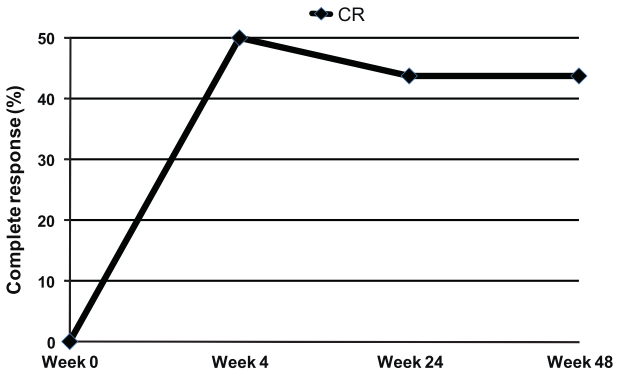

Figure 2 Complete responses were 50% at week 4, and 43.75% at weeks 24 and 48 of patients who had complete responses after 4 weeks, 87.5% continued to exhibit complete responses after 48 weeks.

48 weeks was 43.75%. Once CR was achieved, the recurrence rate was low and the effect of treatment was maintained in 87.5% of patients (Fig. 2). Patients who reached a CR with adalimumab treatment did not require any type of surgical therapy during the study.

Setons were withdrawn from three patients who experienced CR and showed no radiological evidence of severe disease at 24 weeks. In these cases, MRI score decreased from 13.56 ± 4.28 to 5.5 ± 0.58($P < 0.001$; Fig. 3.1.L, 1.R, 2.L and 2.R). In one patient, the seton came out spontaneously. Setons were not removed from three patients who experienced PR.

Patients with complex fistulas who achieved CR had been treated with setons which were removed when both external discharge and resonance inflammation had ceased, maintaining fistula closure at week 48 (Table 3) (Fig. 3.3A, B, C).

During the maintenance therapy two patients (12.5%) required a change of adalimumab therapy to a weekly dose to control a worsening of the inflammatory symptoms and an increase in CDAI at weeks 14 and 20.

One patient with simple fistula who experienced CR developed a new painless active external discharge orifice 12 weeks after commencing treatment. In this case, no response was achieved with the change of adalimumab to a weekly dose, so we decided to withdraw this patient from the study. A new MRI and rectoscopy were performed to establish an alternative therapeutic approach.

No serious complications were associated with adalimumab therapy. 2 of 16 cases developed a psoriasiform dermatitis, which was controlled with single topical treatment. 1 case presented a headache in the first 24 h after adalimumab intake, well controlled with acetamynophen, 650 mg every 6 h orally. Finally, 2 patients consulted by self-limited viriasis of the upper airways, which did not require the withdrawal of adalimumab.

4. Discussion

Fistulizing perianal disease is usually accompanied by morbidity and is difficult to treat. The introduction of infliximab has increased management options and reduced rates of hospital admission and surgery.[20] Although infliximab induction therapy stops fistula discharge in 55% of cases, recurrence of the disease after suspension of treatment is common.[4]

Complex fistulas are associated with a high level of recurrence, poor prognosis, and respond poorly to conventional treatments.[21] Although MRI and echoendoscopy of internal fistula trajectories are 85% reliable, exploration under anaesthesia by an expert surgeon is regarded as the reference procedure.[22] On the other hand, MRI prior to EUA, complements and facilitates surgical management of fistulas and decreases fistula recurrence by 75%.[23] Evaluation and correct anatomical classification of fistulas improve prediction of their courses and treatment responses.

We used MRI to guide therapy in complex fistulas. If MRI revealed the presence of severe or complicated disease, exploration under anaesthesia was carried out by a surgeon who drained the abscesses and inserted loose setons. Patients in whom there was clinical fistula remission, setons were not removed until the fistula was inactive on MRI.

Seton drainage *per se* is effective in reducing symptoms but the rate of the fistula recurrence is 50%.[24,25] Seton placement during clinical treatment promotes fistula healing. A complete response rate of 67%–85% is obtained when induction therapy is combined with infliximab and seton drainage.[8,26,27] Regueiro et al. [10] reported a 100% CR rate after induction with infliximab and a combination of EUA and seton drains, but the long-term recurrence rate was 50%. Combined management improves responses; however, when only clinical data is considered, early seton withdrawal and incorrect infliximab maintenance may contribute to recurrence.

Long-term recurrence is reduced when maintenance of infliximab treatment every 8 weeks is combined with surgical management. Schwartz et al. [8] combined infliximab maintenance therapy with echoendoscopy. Setons were placed in complex fistulas and remission was defined in terms of clinical-radiological criteria. When these criteria are applied, the short-term (12 week) response rate is 86% and the long-term (68 week) response rate is 76%.

In a recent randomized prospective study, the use of EUS to guide the combination of medical and surgical treatments improves the outcomes of fistulizing disease with a durable cessation of drainage from 20% in the control group to 80% in the EUS group.[27]

Maintenance treatment with adalimumab is effective for luminal and fistulizing Crohn's disease.[11–15] Loss of response to infliximab may play a role in the development of fistulas, but more likely, these fistulas developed secondary to an inadequate fistula or abscess drainage. Although the number

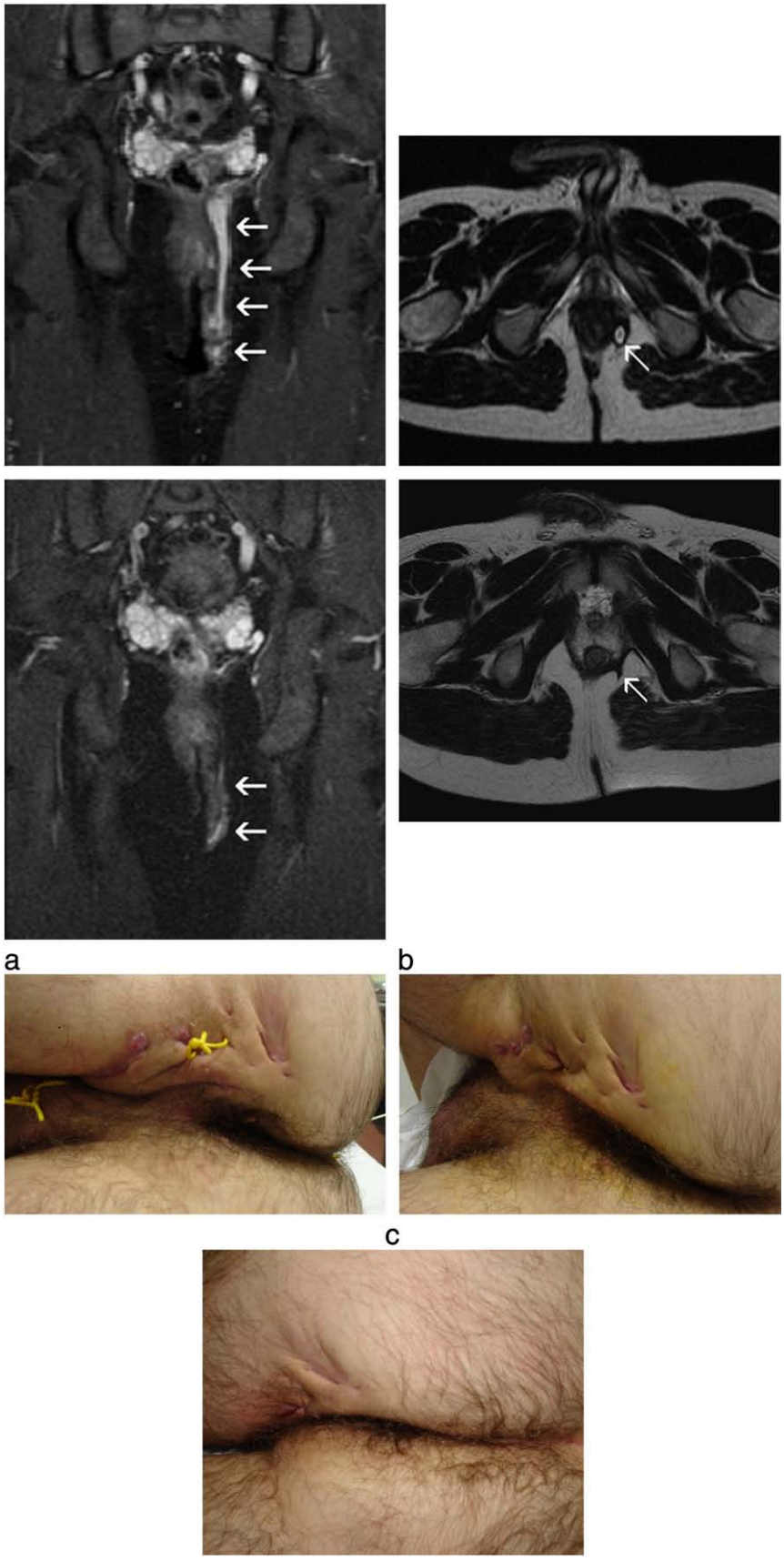

Table 3 Clinical outcome of perianal fistulas: response based on the type of fistula.

Type of fistula	Simple with proctitis (n=7)	Complex (n=9)	Total (n=16)
MRI	-	9	9
EUA	-	7	7
Setons/patient	-	1.3	1.3
CR at 4 weeks	4/7 (57%)	4/9 (44%)	8/16 (50%)
Recurrence rate at 48 weeks	1/4 (25%)	0/9 (0%)	1/8 (12.5%)
Time to recurrence	12 weeks	-	12 weeks
Basal MRI score	-	13.56±4.8	-
CR MRI score	-	5.5±0.8	-

of patients included in our study was modest, we feel it was sufficient to consider that most of the criteria applied to infliximab treatment should be applied to adalimumab treatment. Complex or complicated fistulas in which MRI demonstrates internal trajectory involvement or abscesses require adalimumab maintenance treatment and surgical insertion of seton drains which should only be removed after radiological evidence of the absence of fistula activity. Treatment decisions during the follow-up period including the appropriate time for seton removal or the optimal duration of biological therapy were based on the MRI findings.[27-29]

Our short- and long-term results compare favourably with previous adalimumab fistulas treatment studies. Complete cessation of drainage occurred in 50% of cases in the short-term, and 87.5% was able to maintain this effect over time, with a follow-up of 48 weeks.

Consistent with the results of previous studies,[14,15] response rates were similar between patients who received concomitant therapy with immunosuppressive agents or antibiotics and those who did not. However, consideration must be given to the small sample size included in our study. Further studies are recommended to confirm this preliminary finding.

In our study one patient with simple fistula with proctitis experienced recurrence, suggesting that the simple fistula with bowel inflammation and the complex fistula should be treated in the same multidisciplinary approach especially if patients had a previous history of anti-TNF failure.

Further improvement in these responses could be expected if naïve patients are treated or if all perianal Crohn's disease patients are assessed using standardized MRI or echoendoscopy protocols.

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Manuel Barreiro and Daniel Carpio have made substantial contributions to all of the following: (1) acquisition of data, or analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, and (3) final approval of the version to be submitted.

Santos Pereira and Aurelio Lorenzo have made substantial contributions to all of the following: (1) revising it critically for important intellectual content, (2) drafting the article, and (3) final approval of the version to be submitted.

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Fig. 3 1.L (STIR coronal section) and 1.R (T2 axial section): a long trans-sphincteric perianal fistula with supralevatoric extension. Pronounced hyperintensity on T2-weighted MRI images with fat suppression. 2.L (STIR coronal section) and 2.R (T2 axial section): after 24 weeks of adalimumab therapy, a clear improvement of inflammation in fistula tracks is evident. In the T2 axial section hyperintensity is minimal, but the hypointense track is still evident. 3.A, 3.B and 3.C: treatment follow-up based on clinical and radiological criteria. When cessation of fistulas discharge was accompanied by the absence of radiological activity, setons were removed. Patient in CR before removal of setons (A) and after seton removal at 24 weeks (B) and 48 weeks (C).

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