Systematic review

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Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment

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Abstract

Aim The introduction of anti-tumour necrosis factor (anti-TNF; infliximab and adalimumab) has changed the management of Crohn's perianal fistula from almost exclusively surgical treatment to one with a much larger emphasis on medical therapy. The aim of this systematic review was to provide an overview of the success rates of setons and anti-TNF for Crohn's perianal fistula.

Method Studies evaluating the effect of setons and anti-TNF on Crohn's perianal fistula were included. Studies assessing perianal fistula in children, rectovaginal and rectourinary fistulae were excluded. The primary end-point was the fistula closure rate. Partial closure and recurrence rates were secondary end-points.

Results Ten studies on seton drainage were included ($n = 305$). Complete closure varied from 13.6% to 100% and recurrence from 0% to 83.3%. In 34 anti-TNF studies ($n = 1449$), complete closure varied from 16.7% and 93% (partial closure 8.0–91.2%) and recurrence from 8.0% to 40.9%. Four randomized controlled trials ($n = 1028$) comparing anti-TNF with placebo showed no significant difference in complete or partial closure in meta-analysis (risk difference 0.12, 95% CI −0.06 to 0.30 and 0.09, 95% CI −0.23 to 0.41, respectively). Subgroup analysis ($n = 241$) showed a significant advantage for complete fistula closure with anti-TNF in two trials with follow-up > 4 weeks (46% *vs* 13%, $P = 0.003$ and 30% *vs* 13%, $P = 0.03$). Of four included cohort studies, two revealed a significant difference in response in favour of combined treatment ($P = 0.001$ and $P = 0.014$).

Conclusion Closure and recurrence rates after seton drainage as well as anti-TNF vary widely. Despite a large number of studies, no conclusions can be drawn regarding the preferred strategy. However, combination therapy with (temporary) seton drainage, immunomodulators and anti-TNF may be beneficial in achieving perianal fistula closure.

Keywords Crohn's perianal fistula, seton, anti-TNF

Introduction

Crohn's disease (CD) is a common chronic disease with an incidence rate of 6.9 per 100 000 inhabitants per year in the Netherlands [1]. Perianal fistulation is common in patients with Crohn's disease, the estimated lifetime risk of perianal fistula being between 14% and 38% in population-based estimates [2]. Perianal fistulizing disease is associated with local pain, discharge and considerable morbidity (including destruction of the sphincter and perineal tissue), resulting in a negative impact on quality of life [3]. Unfortunately spontaneous fistula closure rates are low, with estimates ranging from 6% to 13% [4,5].

The management of Crohn's perianal fistulation has historically been surgical, with seton placement being the most frequently used technique. However, since the introduction of anti-tumour necrosis factor (anti-TNF) agents (infliximab and adalimumab), the treatment of Crohn's fistula has changed, with a larger emphasis on medical therapy [6–9].

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This study has been presented at the annual meeting of the United Gastroenterology Week, Vienna 2014, the International Colorectal Forum, Villars 2015 and the Dutch Surgical Days, Veldhoven 2015 and the European Society of Coloproctology 2015.

The purpose of this systematic review was to examine the reported success rate of both seton drainage and anti-TNF agents in patients with perianal Crohn's fistula.

Methods

A systematic review of the literature on seton drainage and anti-TNF (infliximab or adalimumab) for the treatment of perianal fistula in Crohn's disease was performed by two independent researchers (EJG and SS). The present review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [10]. The final search was performed on 15 April 2015.

Databases

MEDLINE, Embase and BIOSIS were searched. No restrictions on publication type were applied and no methodological filter was used.

Search terms

The MeSH terms and free text used in various forms and combinations were assembled with a medical librarian. Two independent searches where performed, one for seton drainage and one for anti-TNF treatment. The terms used in both searches were 'Crohn's disease' or 'Crohn' and 'rectal fistula' or 'fistula'. For the search on seton drainage the term 'seton' was added. For the search on anti-TNF the following terms were added: 'infliximab' or 'remicade' or 'Tumour Necrosis Factor-alpha' or 'Tumour Necrosis Factors' or 'tumour necrosis factor-α' or 'anti-TNF' or 'Cachectin-Tumour Necrosis Factor' or 'cachetin' or 'monoclonal antibody cA2' or 'MAb cA2' or 'adalimumab' or 'humira'. Details are provided in Appendix S1 in the Supporting Information.

Selection

The reviewers separately screened the title and abstract of the retrieved articles. Afterwards they assessed the articles by joint discussion. In the event of disagreement, a third reviewer (CJB) was involved. Studies addressing seton drainage and anti-TNF for treatment of perianal fistula in Crohn's disease were included. In addition, the included articles were hand searched for relevant references. Studies on perianal fistula in children, rectovaginal and rectourinary fistulae and review articles were excluded.

Primary and secondary outcomes

Each study was examined for the primary outcome of interest, complete fistula closure. Secondary outcome parameters were partial closure and recurrence.

Data extraction and statistical analysis

The two reviewers independently extracted data from the studies, and afterwards assessed the results in joint discussion. Statistical analysis was done using Review Manager, version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Two meta-analyses of randomized controlled trials (RCTs) comparing closure rates with anti-TNF therapy *vs* placebo were performed. Pooled effects were presented as risk differences with 95% CIs. Because heterogeneity was expected, the meta-analyses were done *a priori* with the use of a random effects model. Heterogeneity between studies was determined with the I^2 statistic.

Assessment of methodological quality

The methodological quality of the included studies was assessed by the two reviewers separately, using the Cochrane criteria for assessing risk of bias in RCTs. For cohort studies and case series, elements of the STROBE checklist were used (Table S1) [11]. To assess the risk of bias, the following key elements were assessed: selection bias/confounding (consecutive or random inclusion, avoidance of inappropriate inclusion and exclusion, adequate description of the source of the patients, adequate description of baseline characteristics, description of confounders, whether potential confounders accounted for in the analyses), performance bias (impact of a concurrent intervention, fidelity to the intervention protocol), attrition bias (handling of missing data), detection bias (follow-up, blinding, proper description of the procedure, clear definition of outcome parameters) and reporting bias (prespecification of potential outcomes, reporting of all prespecified outcomes). Risk of bias was scored as high, low or uncertain, and a total risk was calculated. If there was a high risk score for one or more key elements within a study, the overall risk was scored as high.

In addition, generalizability was assessed and graded based on the methodological design (multicentre or single-centre studies, patient population, sample size and follow-up) of the studies and overall scored as high, low or uncertain.

Results

Study selection process for seton drainage

The initial literature search for seton drainage identified 313 studies after removal of duplicates. Subsequently, titles and abstracts were screened, after which 74 potentially eligible publications remained. After full-text review of these publications, ten studies, mainly case series, met the inclusion criteria and presented the primary or one secondary outcome parameter [12–21]. These studies were included in the analysis for treatment with seton drainage (Fig. 1).

Study selection process for anti-TNF

There were 1888 hits after duplicates were removed. After subsequent screening of titles and abstracts, 249 potentially eligible articles remained. Eventually, after full-text review, 42 studies remained (Fig. 2). Four RCTs comparing anti-TNF therapy regimens with placebo were included in a meta-analysis and reported separately [4,22–24]. Also, four studies directly comparing (combined) anti-TNF and seton drainage on closure and recurrence rates were analysed separately [25–28]. Finally, 34 cohort studies and case-series on anti-TNF treatment were analysed [6,8,9,29–59].

Patient population and outcome analysis for seton drainage

Overall, 305 patients with Crohn's disease were treated with seton drainage for their perianal fistulae (Table S2).

Complete closure was reported in five studies; the rates varied between 13.6% and 100%. Among the included studies the single cohort study (retrospective) by Chung *et al.* [12], mentioned a complete closure rate of 31.3%. Partial closure was not reported in any of

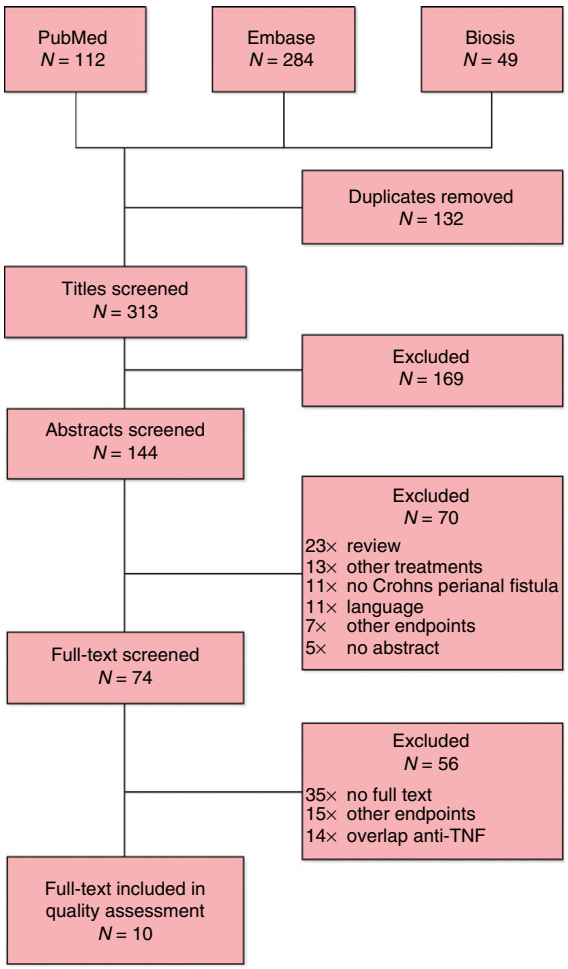

Figure 1 Flowchart of seton drainage search.

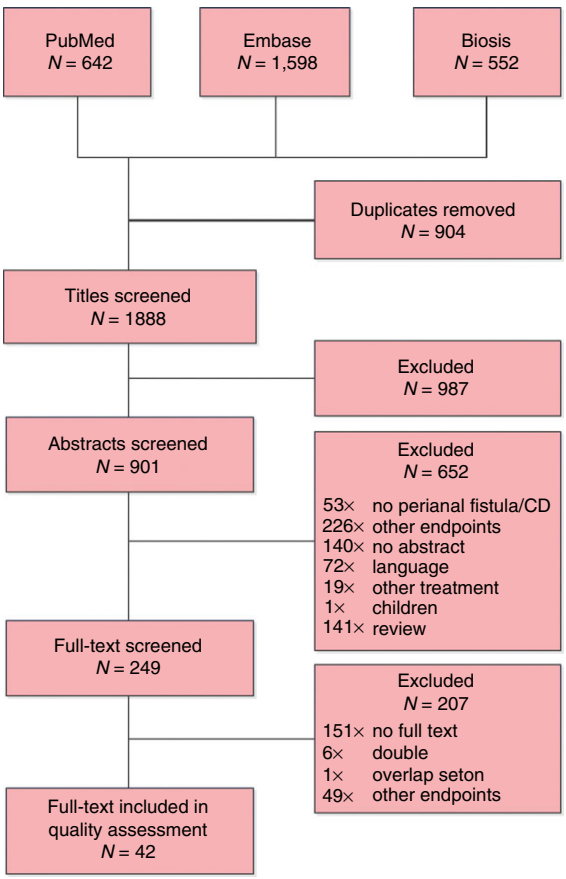

Figure 2 Flowchart for anti-TNF search.

these studies. Recurrence rates were reported by eight studies, and varied from 0% to 83.3%. The only included prospective cohort study by Shinozaki *et al.* [18] reported a recurrence rate of 33.3%. Timing of seton removal differed among the studies (from 3 weeks to 40 months). Because of the considerable heterogeneity among the studies no meta-analysis was performed.

Patient population and outcome analysis for anti-TNF

A total of 1449 patients with perianal fistula were treated with anti-TNF medication (Table S3). There were 22 studies assessing infliximab treatment, eight studies on adalimumab and four on both infliximab and adalimumab without comparison with placebo. There were articles on induction as well as on maintenance therapy. Follow-up differed widely between the studies, where some assessed the end-point at only 8 weeks, others had a mean follow-up of almost 5 years.

Complete closure rates were reported by all 34 studies and varied between 16.7% and 93%. Partial closure was described by 21 studies (8.0–91.2%) (Table S3). Among these studies one RCT by Dewint *et al.* [31] was included. In this study complete and partial closure rates were 43% and 54%, respectively, after 24 weeks of follow-up. Recurrence rates were only mentioned by 11 studies (8.0–40.9%) (Table S3).

Patient population and outcome analysis for studies directly comparing (combined) anti-TNF and seton drainage

Four cohort studies directly compared combined therapy with anti-TNF (infliximab) treatment and/or seton drainage alone for patients with Crohn's perianal fistula (Table S4) [25–28]. These studies mainly had a retrospective design, except for the study of Sciaudone *et al.* [27]. Anti-TNF treatment has been administered to 132 patients in total, of whom 98 were simultaneously treated with seton drainage. Overall, 109 patients were treated with seton drainage without anti-TNF. Follow-up ranged from 15 weeks to a mean of 30 months. Complete closure rates for combined therapy varied widely (0–100%). In the study reporting zero complete fistula closures it was unclear whether the setons were removed [26]. Partial closure rates were only described by two studies for this treatment strategy (14.3–88.5%) [26,27]. Gaertner *et al.* [28] reported a significant difference in response rates between combined treatment *vs* seton drainage without anti-TNF of 45% *vs* 17%, respectively ($P = 0.001$), whereas Regueiro and Mardini [25] showed a significant difference between combined treatment *vs* anti-TNF therapy without seton drainage of 100% *vs* 82.6%, respectively ($P = 0.014$). Recurrence was described by two studies, of which one showed a significant difference in favour of combined treatment when compared with anti-TNF therapy without seton drainage (44.4% *vs* 78.9% respectively; $P = 0.001$) [25].

Meta-analyses for anti-TNF

Four RCTs comparing anti-TNF regimens with placebo were included in the meta-analysis: one study on infliximab and three studies analysing adalimumab (CLASSIC, CHARM and GAIN trials) [4,22–24] (Table S5). Patients with all kinds of fistulizing disease were included in these trials (perianal, enterocutaneous and enteroenteral fistulae). Patients treated with either 5 mg/kg infliximab or 40–80 mg adalimumab were included in the meta-analysis since this is the recommended dose in several guidelines [60]. Seton insertion for perianal fistula was not mentioned in any of the RCTs. In total, 179 patients were treated with anti-TNF medication whereas 109 patients received placebo. All studies assessed complete closure rates and three studies reported partial closure rates. Recurrence rates were not reported. The mean follow-up time was 13 weeks (range 4–26).

In the anti-TNF group, 54 of 179 (30%) patients responded to treatment with complete fistula closure, whereas complete closure was seen in 13 of 109 (12%) patients in the placebo group. Partial fistula closure was seen in 48 of 109 (44%) patients in the anti-TNF group and in 15 of 62 (24%) patients in the placebo group. There was no significant difference in complete or partial closure rates between the groups [risk difference (RD) 0.12, 95% CI −0.06 to 0.30, $I^2 = 74\%$; and RD 0.09, 95% CI −0.23 to 0.41, $I^2 = 78\%$, respectively) (Figs 3 and 4). As heterogeneity among the studies was high, a random-effects model was used to estimate the pooled total effect. Due a lack of Kaplan–Meier curves for fistula closure in the included studies, only dichotomous data were used and risk differences were reported.

A subgroup analysis for complete fistula closure was performed based on studies with a follow-up longer than 4 weeks. This showed a significant advantage for complete fistula closure with anti-TNF in the two trials with follow-up longer than 4 weeks (Present *et al.* [4], 46% *vs* 13%, $P = 0.003$; CHARM [23], 30% *vs* 13%, $P = 0.043$).

Study quality and shortcomings

Studies on seton drainage were solely (prospective and retrospective) cohort studies and case series, mainly of questionable quality (Table S6). Among the studies on

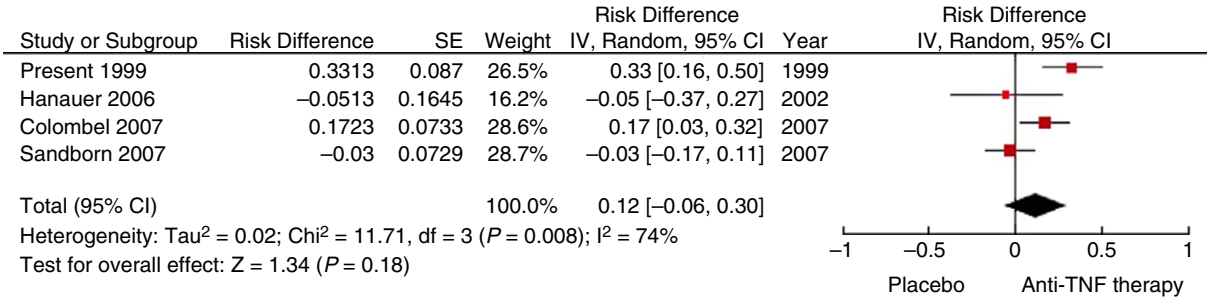

Figure 3 Meta-analysis of four randomized controlled trials comparing anti-TNF therapy with placebo for complete fistula closure.

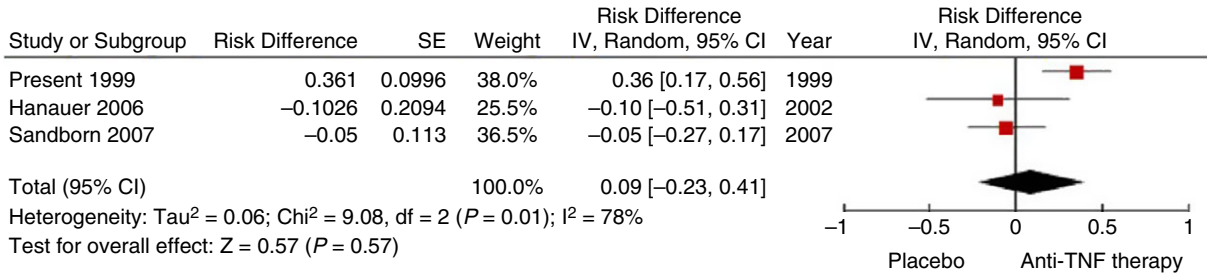

Figure 4 Meta-analysis of three randomized controlled trials comparing anti-TNF therapy with placebo for partial fistula closure.

anti-TNF there were six RCTs (of which four were included in the meta-analysis), eight cohort studies and 21 case series.

The methodological quality of the RCTs was high overall, whereas the quality of the cohort studies and case series was questionable (Tables S7–S9). The RCTs included in the meta-analysis were all funded by pharmaceutical companies.

Generalizability was less high for the RCTs, since stricter inclusion criteria were applied. Cohort studies and case series mainly focused on a more general population. Details on the patient population, procedure description and end-point definitions for each study are provided in Tables S10–S13.

Discussion

Based on the results of this systematic literature review it can be concluded that closure and recurrence rates after treatment with seton drainage as well as with anti-TNF vary widely.

The studies that reported on seton drainage alone had several limitations. First of all, the included cohort studies and case series were mainly of questionable quality. One of the cohort studies on seton drainage with the highest fistula closure rate is over 20 years old, with a very small sample size ($n = 6$) [21]. In addition, the most recent study (with 31.3% closure) assessed this outcome parameter after only 3 months, which is too short a time for a meaningful follow-up [12]. Secondly, in all studies, seton removal was at the discretion of the treating physician, which could introduce information bias. Since complete closure of the internal opening can only be achieved after seton removal, the fact that in some studies seton removal was not reported could introduce detection bias. The duration of seton drainage differed in the reported studies, and it remains unclear what the optimal timing for seton removal should be.

In the studies included, the definition of complete healing differed among studies or was not further defined. This was mainly the case in studies reporting on seton drainage (Tables S10–S13). In the majority of studies, closure was assessed by physical examination by the treating physician, which may have introduced a measurement bias. Only a few studies MRI used to assess closure of the fistula tracts.

When addressing the limitations of the studies of anti-TNF it must be emphasized that although overall a large group of patients were treated with anti-TNF, some studies only had a small sample of patients with Crohn's perianal fistula within the study group. In addition, the follow-up time varied widely between the studies. Whereas some studies were focusing on induction therapy, others were aiming for maintenance therapy. In several studies the end-points were

assessed after only 8–12 weeks (induction), which is too soon. This was also supported by the meta-analysis of the four RCTs included, which did not show a significant advantage for (complete or partial) fistula closure with anti-TNF as compared with placebo. However, subgroup analysis did show an advantage on complete fistula closure rates for anti-TNF treatment in the two trials with a follow-up longer than 4 weeks. Although closure rates with anti-TNF are disappointing, it is currently the most effective medical therapy for patients with *inflammatory bowel disease* refractory to standard medication. During the past decade more knowledge has been gained with respect to adequate dosing of anti-TNF by monitoring treatment effect and measuring trough levels [61]. Concomitant immunomodulating therapy can decrease the formation of antibodies to anti-TNF and may improve long-term outcome [62]. Since fistulizing Crohn's disease is a chronic condition, long-term results are of crucial importance. The long-term results of the CHARM trial demonstrated that all patients with complete fistula closure at week 26 continued to have complete fistula closure at week 56 when medication was not stopped. Long-term results of the ACCENT II trial have showed complete fistula closure in 34% of patients responding to infliximab therapy after 46 weeks *vs* 19% closure in the placebo group [63]. Since patients in this study were randomized after 14 weeks of infliximab treatment, it was not included in the meta-analysis. In addition, patients with rectovaginal fistula were included in the study by Sands *et al.* [63], which is an exclusion criterion for the present review. However, Lichtenstein *et al.* [64] showed that the median length of time during which fistulae remained closed after cessation of medication was 3 months, with over 50% reopening of the fistula. It remains unclear how long anti-TNF should be continued for sustained fistula closure.

The additional use of seton drainage prior to anti-TNF treatment varied among the studies. In cases of perianal sepsis, adequate seton drainage of a fistula is of key importance prior to starting anti-TNF medication. The available cohort series suggest that combining seton drainage with anti-TNF therapy is superior to either therapy alone. The results of this systematic review are in keeping with a systematic review by Yassin *et al.* [65], who also found that a combination of surgical treatments (including seton drainage as well as other surgical treatments) with medical therapy (anti-TNF and immunomodulators) may have additional benefit on healing of perianal fistula in patients with Crohn's disease compared with surgery or medical therapy alone. To date, there are no published RCTs comparing seton drainage and anti-TNF for Crohn's perianal fistulae directly. Furthermore, many patients were simultaneously treated with immunomodulators or other immunosuppressive medication. The use of concomitant medical therapy was reported in most studies, although it was not considered as a potential confounder in these series.

In this review it was intended to limit the analysis to closure rates and recurrences in perianal fistulae only in order to avoid selection bias. Therefore, data on rectovaginal or rectourinary fistulae were excluded where possible. However, the RCTs included in the meta-analysis comparing anti-TNF with placebo did not distinguish between perianal, enterocutaneous and enteroenteral fistulae. It was not possible to extract specific data on perianal fistulae alone, which was recognized as a severe limitation. However, it is likely that the majority of fistulae were of perianal origin, since these are much more common than enterocutaneous fistulae in Crohn's disease. In the study by Present *et al.* [4], the percentage of patients with perianal fistulae was 90% compared with 10% with enterocutaneous fistulae.

Currently, with the development of new biologicals (e.g. vedolizumab) there are more medical treatment options nowadays. In a recent randomized controlled trial assessing the efficacy of vedolizumab, perianal fistulas closed in 17 patients (23%) treated with vedolizumab every 8 weeks and 22 patients (41%) with vedolizumab every 4 weeks compared to 18 patients (11%) in the placebo group ($P = 0.32$ and $P = 0.03$) [66].

In view of the limitations of the included studies and the drawbacks encountered in this systematic review, a well-designed clinical trial directly comparing seton drainage and anti-TNF therapy is warranted. Clear end-point definitions and procedural descriptions are essential. It is also imperative that follow-up should be long enough to comment on recurrence rates after primary closure of the perianal fistula. The currently recruiting PISA trial may answer some of these questions. PISA is an 18-centre multinational (NTR4137) randomized parallel group trial comparing chronic seton drainage alone with 1-year anti-TNF with seton drainage or seton drainage followed by 4 months' anti-TNF treatment together with advancement plasty [67]. The primary end-point in that study is the proportion of patients with reinterventions.

In summary, closure and recurrence rates after treatment with seton drainage as well as with anti-TNF vary widely. Despite a large number of studies analysing the results of both treatment options, no conclusion can be drawn regarding the preferred strategy. However, com-

bination therapy with (temporary) seton drainage, an immunomodulator and anti-TNF may be beneficial in achieving closure of perianal fistulae.

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EJG drafted the manuscript. SS, CL, CYP and WAB co-authored the writing of the manuscript. All authors edited the manuscript and read and approved the final manuscript.

Conflicts of interest

This work was not supported by any grant or company. The authors declare no conflict of interest.

References

1 Russel MG, Dorant E, Volovics A *et al.* High incidence of inflammatory bowel disease in The Netherlands: results of a prospective study. The South Limburg IBD Study Group. *Dis Colon Rectum* 1998; **41:** 33–40.
2 Hellers G, Bergstrand O, Ewerth S, Holmstrom B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. *Gut* 1980; **21:** 525–7.
3 Vigano C, Losco A, Caprioli F, Basilisco G. Incidence and clinical outcomes of intersphincteric abscesses diagnosed by anal ultrasonography in patients with crohn's disease. *Inflamm Bowel Dis* 2011; **17:** 2102–8.
4 Present DH, Rutgeerts P, Targan S *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340:** 1398–405.
5 Present DH, Korelitz BI, Wisch N *et al.* Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302:** 981–7.
6 Arnott ID, McDonald D, Williams A, Ghosh S. Clinical use of Infliximab in Crohn's disease: the Edinburgh experience. *Aliment Pharmacol Ther* 2001; **15:** 1639–46.
7 Ardizzone S, Colombo E, Maconi G *et al.* Infliximab in treatment of Crohn's disease: the Milan experience. *Dig Liver Dis* 2002; **34:** 411–8.
8 Poritz LS, Rowe WA, Koltun WA. Remicade does not abolish the need for surgery in fistulizing Crohn's disease. *Dis Colon Rectum* 2002; **45:** 771–5.
9 Orlando A, Colombo E, Kohn A *et al.* Infliximab in the treatment of Crohn's disease: predictors of response in an Italian multicentric open study. *Dig Liver Dis* 2005; **37:** 577–83.
10 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339:** b2535.
11 Viswanathan M, Ansari MT, Berkman ND *et al.* Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. 2008.
12 Chung W, Ko D, Sun C *et al.* Outcomes of anal fistula surgery in patients with inflammatory bowel disease. *Am J Surg* 2010; **199:** 609–13.
13 Galis-Rozen E, Tulchinsky H, Rosen A *et al.* Long-term outcome of loose seton for complex anal fistula: a two-centre study of patients with and without Crohn's disease. *Colorectal Dis* 2010; **12:** 358–62.
14 Higashi D, Futami K, Egawa Y *et al.* Infliximab treatment for anal fistula in patients with Crohn's disease. *Anticancer Res* 2009; **29:** 927–33.
15 Thornton M, Solomon MJ. Long-term indwelling seton for complex anal fistulas in Crohn's disease. *Dis Colon Rectum* 2005; **48:** 459–63.
16 Buchanan GN, Owen HA, Torkington J *et al.* Long-term outcome following loose-seton technique for external sphincter preservation in complex anal fistula. *Br J Surg* 2004; **91:** 476–80.
17 Takesue Y, Ohge H, Yokoyama T *et al.* Long-term results of seton drainage on complex anal fistulae in patients with Crohn's disease. *J Gastroenterol* 2002; **37:** 912–5.
18 Shinozaki M, Koganei K, Fukushima T. Simultaneous anus and bowel operation is preferable for anal fistula in Crohn's disease. *J Gastroenterol* 2002; **37:** 611–6.
19 Makowiec F, Jehle EC, Becker HD, Starlinger M. Perianal abscess in Crohn's disease. *Dis Colon Rectum* 1997; **40:** 443–50.
20 Williams JG, Rothenberger DA, Nemer FD, Goldberg SM. Fistula-in-ano in Crohn's disease. Results of aggressive surgical treatment. *Dis Colon Rectum* 1991; **34:** 378–84.
21 Morrison JG, Gathright JB Jr, Ray JE *et al.* Surgical management of anorectal fistulas in Crohn's disease. *Dis Colon Rectum* 1989; **32:** 492–6.
22 Hanauer SB, Sandborn WJ, Rutgeerts P *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130:** 323–33.
23 Colombel JF, Sandborn WJ, Rutgeerts P *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132:** 52–65.
24 Sandborn WJ, Rutgeerts P, Enns R *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007; **146:** 829–38.
25 Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis* 2003; **9:** 98–103.
26 Uchino M, Ikeuchi H, Bando T *et al.* Long-term efficacy of infliximab maintenance therapy for perianal Crohn's disease. *World J Gastroenterol* 2011; **17:** 1174–9.
27 Sciaudone G, Di SC, Limongelli P *et al.* Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach. *Can J Surg* 2010; **53:** 299–304.
28 Gaertner WB, Decanini A, Mellgren A *et al.* Does infliximab infusion impact results of operative treatment for

Crohn's perianal fistulas? *Dis Colon Rectum* 2007; **50:** 1754–60.
29 Guidi L, Ratto C, Semeraro S *et al.* Combined therapy with infliximab and seton drainage for perianal fistulizing Crohn's disease with anal endosonographic monitoring: a single-centre experience. *Tech Coloproctol* 2008; **12:** 111–7.
30 Bouguen G, Siproudhis L, Gizard E *et al.* Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol* 2013; **11:** 975–81.
31 Dewint P, Hansen BE, Verhey E *et al.* Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut* 2014; **63:** 292–9.
32 Antakia R, Shorthouse AJ, Robinson K, Lobo AJ. Combined modality treatment for complex fistulating perianal Crohn's disease. *Colorectal Dis* 2013; **15:** 210–6.
33 Duff S, Sagar PM, Rao M *et al.* Infliximab and surgical treatment of complex anal Crohn's disease. *Colorectal Dis* 2012; **14:** 972–6.
34 El-Gazzaz G, Hull T, Church JM. Biological immunomodulators improve the healing rate in surgically treated perianal Crohn's fistulas. *Colorectal Dis* 2012; **14:** 1217–23.
35 Fortea-Ormaechea JI, Gonzalez-Lama Y, Casis B *et al.* Adalimumab is effective in long-term real life clinical practice in both luminal and perianal Crohn's disease. The Madrid experience. *Gastroenterol Hepatol* 2011; **34:** 443–8.
36 Karmiris K, Bielen D, Vanbeckevoort D *et al.* Long-term monitoring of infliximab therapy for perianal fistulizing Crohn's disease by using magnetic resonance imaging. *Clin Gastroenterol Hepatol* 2011; **9:** 130–6.
37 Savoye-Collet C, Savoye G, Koning E, Dacher JN, Lerebours E. Fistulizing perianal Crohn's disease: contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF-alpha therapy. *Inflamm Bowel Dis* 2011; **17:** 1751–8.
38 Echarri A, Castro J, Barreiro M *et al.* Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure. *J Crohns Colitis* 2010; **4:** 654–60.
39 Gligorijevic V, Spasic N, Bojic D *et al.* The role of pelvic MRI in assesment of combined surgical and infliximab treatment for perianal Crohn's disease. *Acta Chir Iugosl* 2010; **57:** 89–95.
40 Miheller P, Lakatos PL, Horvath G *et al.* Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe–a Hungarian nationwide observational study. *BMC Gastroenterol* 2009; **9:** 66.
41 Ng SC, Plamondon S, Gupta A, Burling D, Kamm MA. Prospective assessment of the effect on quality of life of anti-tumour necrosis factor therapy for perineal Crohn's fistulas. *Aliment Pharmacol Ther* 2009; **30:** 757–66.
42 Oussalah A, Babouri A, Chevaux JB *et al.* Adalimumab for Crohn's disease with intolerance or lost response to infliximab: a 3-year single-centre experience. *Aliment Pharmacol Ther* 2009; **29:** 416–23.
43 Tougeron D, Savoye G, Savoye-Collet C *et al.* Predicting factors of fistula healing and clinical remission after infliximab-based combined therapy for perianal fistulizing Crohn's disease. *Dig Dis Sci* 2009; **54:** 1746–52.
44 Trinder MW, Lawrance IC. Efficacy of adalimumab for the management of inflammatory bowel disease in the clinical setting. *J Gastroenterol Hepatol* 2009; **24:** 1252–7.
45 Lopez PN, Mendoza JL, Taxonera C *et al.* Adalimumab induction and maintenance therapy for Crohn's disease. An open-label study. *Rev Esp Enferm Dig* 2008; **100:** 676–81.
46 Spradlin NM, Wise PE, Herline AJ *et al.* A randomized prospective trial of endoscopic ultrasound to guide combination medical and surgical treatment for Crohn's perianal fistulas. *Am J Gastroenterol* 2008; **103:** 2527–35.
47 Hinojosa J, Gomollon F, Garcia S *et al.* Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open-label, multicentre trial. *Aliment Pharmacol Ther* 2007; **25:** 409–18.
48 Hyder SA, Travis SP, Jewell DP, McC Mortensen NJ, George BD. Fistulating anal Crohn's disease: results of combined surgical and infliximab treatment. *Dis Colon Rectum* 2006; **49:** 1837–41.
49 Ardizzone S, Maconi G, Colombo E *et al.* Perianal fistulae following infliximab treatment: clinical and endosonographic outcome. *Inflamm Bowel Dis* 2004; **10:** 91–6.
50 Luna-Chadid M, Perez Calle JL, Mendoza JL *et al.* Predictors of response to infliximab in patients with fistulizing Crohn's disease. *Rev Esp Enferm Dig* 2004; **96:** 379–81.
51 Rasul I, Wilson SR, MacRae H, Irwin S, Greenberg GR. Clinical and radiological responses after infliximab treatment for perianal fistulizing Crohn's disease. *Am J Gastroenterol* 2004; **99:** 82–8.
52 Schroder O, Blumenstein I, Schulte-Bockholt A, Stein J. Combining infliximab and methotrexate in fistulizing Crohn's disease resistant or intolerant to azathioprine. *Aliment Pharmacol Ther* 2004; **19:** 295–301.
53 Bell SJ, Halligan S, Windsor AC *et al.* Response of fistulating Crohn's disease to infliximab treatment assessed by magnetic resonance imaging. *Aliment Pharmacol Ther* 2003; **17:** 387–93.
54 Topstad DR, Panaccione R, Heine JA *et al.* Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. *Dis Colon Rectum* 2003; **46:** 577–83.
55 Ochsenkuhn T, Goke B, Sackmann M. Combining infliximab with 6-mercaptopurine/azathioprine for fistula therapy in Crohn's disease. *Am J Gastroenterol* 2002; **97:** 2022–5.
56 Farrell RJ, Shah SA, Lodhavia PJ *et al.* Clinical experience with infliximab therapy in 100 patients with Crohn's disease. *Am J Gastroenterol* 2000; **95:** 3490–7.

57 Castano-Milla C, Chaparro M, Saro C *et al.* Effectiveness of adalimumab in perianal fistulas in crohn's disease patients naive to anti-TNF therapy. *J Clin Gastroenterol* 2015; **49:** 34–40.
58 Yang BL, Chen YG, Gu YF *et al.* Long-term outcome of infliximab combined with surgery for perianal fistulizing Crohn's disease. *World J Gastroenterol* 2015; **21:** 2475–82.
59 Kotze PG, de Albuquerque IC, Moreira AL *et al.* Perianal complete remission with combined therapy (seton placement and anti-TNF agents) in Crohn's disease: a Brazilian multicenter observational study. *Arq Gastroenterol* 2014; **51:** 284–9.
60 Van AG, Dignass A, Reinisch W *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; **4:** 63–101.
61 Paul S, Del TE, Marotte H *et al.* Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2013; **19:** 2568–76.
62 Hanauer SB, Wagner CL, Bala M *et al.* Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004; **2:** 542–53.
63 Sands BE, Blank MA, Diamond RH, Barrett JP, van Deventer SJ. Maintenance infliximab does not result in increased abscess development in fistulizing Crohn's disease: results from the ACCENT II study. *Aliment Pharmacol Ther* 2006; **23:** 1127–36.
64 Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005; **128:** 862–9.
65 Yassin NA, Askari A, Warusavitarne J *et al.* Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. *Aliment Pharmacol Ther* 2014; **40:** 741–9.
66 Sandborn WJ, Feagan BG, Rutgeerts P *et al.* Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369:** 711–21.
67 de Groof EJ, Buskens CJ, Ponsioen CY *et al.* Multimodal treatment of perianal fistulas in Crohn's disease: seton versus anti-TNF versus advancement plasty (PISA): study protocol for a randomized controlled trial. *Trials* 2015; **16:** 366.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Key-elements used for assessing risk of bias of cohort studies and case series [11].

Table S2. Characteristics of included studies on seton drainage.

Table S3. Characteristics of included studies on anti-TNF.

Table S4. Characteristics of included cohort studies directly comparing (combined) anti-TNF and seton drainage on closure and recurrence rates of perianal fistulae.

Table S5. Characteristics of included randomized controlled trials in meta-analysis on anti-TNF treatment.

Table S6. Overview of risk of bias and quality assessment of cohort studies and case series on seton drainage.

Table S7. Overview of risk of bias and quality assessment of randomized controlled trials comparing anti-TNF and placebo.

Table S8. Overview of risk of bias and quality assessment of cohort studies directly comparing (combined) anti-TNF and seton drainage.

Table S9. Overview of risk of bias and quality assessment of cohort studies and case series on anti-TNF.

Table S10. Risk of bias and quality assessment of cohort studies and case series on seton drainage.

Table S11. Risk of bias and quality assessment of randomized controlled trials comparing anti-TNF and placebo.

Table S12. Risk of bias and quality assessment of cohort studies directly comparing (combined) anti-TNF and seton drainage.

Table S13. Risk of bias and quality assessment of cohort studies and case series on anti-TNF.

Appendix S1. Search terms.