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ABOUT COVER

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OPINION REVIEW

Approach to medical therapy in perianal Crohn's disease

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Abstract

Perianal Crohn's disease remains a challenging condition to treat and can have a substantial negative impact on quality of life. It often requires combined surgical and medical interventions. Anti-tumor necrosis factor (anti-TNF) therapy, including infliximab and adalimumab, remain preferred medical therapies for perianal Crohn's disease. Infliximab has been shown to be efficacious in improving fistula closure rates in randomized controlled trials. Clinicians can be faced with a number of questions relating to the optimal use of anti-TNF therapy in perianal Crohn's disease. Specific issues include evaluation for the presence of perianal sepsis, the treatment target of therapy, the ideal time to commence treatment, whether additional medical therapy should be used in conjunction with anti-TNF therapy, and the duration of treatment. This article will discuss key studies which can assist clinicians in addressing these matters when they are considering or have already commenced anti-TNF therapy for the treatment of perianal Crohn's disease. It will also discuss current evidence regarding the use of vedolizumab and ustekinumab in patients who are failing to achieve a response to anti-TNF therapy for perianal Crohn's disease. Lastly, new therapies such as local injection of mesenchymal stem cell therapy will be discussed.

Key Words: Fistula; Biologics; Inflammatory bowel disease; Surgery; Stem cells; Infliximab; Ustekinumab

Core Tip: Early commencement of anti-tumor necrosis factor (anti-TNF) therapy in perianal Crohn's disease is preferred over delaying treatment, although perianal sepsis should be treated first. Symptomatic remission remains the treatment goal, with

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radiographic healing an evolving target. Concomitant antibiotic therapy while initiating anti-TNF therapy is efficacious. Therapeutic drug monitoring and dose adjustment of anti-TNF therapy, targeting a higher trough level than what is routinely used for luminal disease, may improve treatment response. Ustekinumab may be efficacious in anti-TNF refractory individuals, although more studies are needed. Mesenchymal stem cell injection can be used in individuals who are refractory to anti-TNF therapy.

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INTRODUCTION

Perianal Crohn's disease is a debilitating complication of Crohn's disease, occurring in up to 30% of individuals with luminal disease[1-3]. It remains a difficult condition to treat, with relapses occurring frequently, and it is associated with a higher rate of hospitalization and surgery compared to individuals with Crohn's disease without perianal disease[4-6]. Perianal Crohn's disease is also associated with a significant burden on quality of life with far reaching consequences on the well-being of an individual, including affecting social relationships and work-related opportunities[7]. Treatment often requires multimodal therapy with surgical treatment and systemic medical therapy used in combination, and this has been shown to be more efficacious than either strategy alone[8,9]. Significant advancements have been made in recent times with surgical and local therapy for perianal disease, with local injections of mesenchymal stem cell therapy showing remarkable promise in randomized studies [10,11]. Despite the advancements in surgical techniques and local therapy in perianal disease and the plethora of medical therapies that are being explored for the treatment of luminal Crohn's disease, systemic medical therapy in perianal Crohn's disease has been dominated by anti-tumor necrosis factor (TNF) therapy, which was shown to be efficacious over two decades ago[12]. Infliximab is the only biologic treatment that has been proven efficacious in a dedicated randomized placebo-controlled trial in individuals with symptomatic perianal Crohn's disease.

While the efficacy of anti-TNF therapy has been established, there is a wide variation in the management of perianal Crohn's disease amongst treating clinicians [13]. This may partially relate to the fact that there are a number of situations that the treating clinician may encounter that are not addressed by randomized studies and where evidence is either insufficient or evolving. These include the timing and duration of anti-TNF therapy, the need for concomitant or increased dose of therapy and what alternative biologics can be used in an individual who is failing anti-TNF therapy. While conclusive data may not be available in many of these situations, there are studies that have been conducted that may provide further insight into decision making in these situations. The aim of this paper, therefore, is to address these potential questions that may assist treating clinicians who are considering medical therapy or have commenced anti-TNF therapy for the treatment of perianal Crohn's disease.

WHAT MODALITIES SHOULD I USE TO EVALUATE PERIANAL CROHN'S DISEASE PRIOR TO COMMENCING ANTI-TNF THERAPY?

An important component of medical therapy when treating perianal Crohn's disease is to control underlying infection prior to commencing immunosuppressive therapy. There are several modalities that can be utilized to evaluate for the presence of a perianal abscess or deep infection, including examination under anesthesia (EUA), magnetic resonance imaging (MRI) pelvis and transrectal ultrasound (TRUS). All modalities have been shown to correctly classify Crohn's perianal fistulae in over 85% of patients and when two modalities are used, the accuracy approaches 100%[14].

Transperineal ultrasound, which is a non-invasive and relatively cheaper modality of imaging, has also been shown to have similar accuracy to TRUS and MRI pelvis in diagnosing perianal fistulae[15]. If available, pelvic MRI provides the most comprehensive evaluation of the perianal region (Figure 1). Small field of view images accurately depict even the most complex fistulous tracts as well as the size, number and location of an abscess cavities including disease extending above the levator ani musculature. Associated features, such as rectal inflammation and lymphadenopathy, can also be seen. Use of one or more of these forms of diagnostic imaging or an EUA should be performed prior to commencing medical therapy with an anti-TNF for the treatment of perianal Crohn's disease.

WHEN IS THE BEST TIME TO COMMENCE ANTI-TNF THERAPY IN PERIANAL CROHN'S DISEASE?

A retrospective claims-based study evaluated the role of early use of immunosuppressive therapies in reducing the risk of developing future perianal disease amongst indi-viduals with a new diagnosis of Crohn's disease. In this study, individuals with a new diagnosis of Crohn's disease without perianal disease exposed to at least 90 days of immunosuppressants or anti-TNF therapy had a 59% reduction in risk, compared to those not using these agents, of developing symptomatic perianal disease over 2 years [16]. While these results require further validation, this study raises the possibility that individuals who are identified as having perianal disease may benefit from earlier medical therapy with immunosuppressive or anti-TNF therapy even if they are minimally symptomatic.

In contrast to these findings, data would suggest that there is often a significant delay in the commencement of biologic therapy in patients with perianal Crohn's disease, with a median of over 6 months between the initial diagnosis of perianal Crohn's disease and the commencement of anti-TNF therapy[17]. The concern for worsening perianal infection may partially explain this delay of immunosuppressive treatment. A retrospective study compared fistula recurrence rates amongst 76 individuals with perianal Crohn's disease who were either started on infliximab late (median, 250 days) or early (median, 12 days) after seton insertion for perianal Crohn's disease[18]. Recurrence rates were low in both groups of this study (8% overall), and no difference was found between early and late commencement of infliximab and no reports of abscesses or perianal sepsis in either group.

A multicenter randomized study assigned patients with newly diagnosed and recurrent perianal Crohn's disease with a seton inserted and fistula drainage to one of three groups: chronic fistula drainage for 12 months, anti-TNF therapy (adalimumab or infliximab) for 12 months with removal of seton at 6 weeks, or initial anti-TNF therapy followed by surgical closure of the fistula within 8 weeks to 12 weeks[19]. The study was initially designed to show superiority of seton insertion in reducing future surgical procedures, but was stopped early due to futility, as the chronic seton group showed a significantly higher rate of fistula re-intervention compared to both the anti-TNF therapy and the surgical closure after anti-TNF therapy groups (74% *vs* 42% *vs* 23%, respectively, $P = 0.02$). Serious adverse events were numerically higher in the anti-TNF group than the chronic seton group (36% *vs* 21%), but the nature of the events and the rate of infection are not described. Overall, these would suggest that early anti-TNF therapy following seton insertion can be utilized for perianal Crohn's disease.

WHAT SHOULD BE THE TARGET OF TREATMENT?

There has been work to establish a consensus on the most appropriate treatment targets in inflammatory bowel disease, given the variability in treatment outcomes that has been reported in clinical trials, and the fact that treatment goals have evolved and become more stringent with the availability of an increasing number of efficacious therapies. A core outcome set in perianal disease was developed by consensus collaboration between key stakeholders in the United Kingdom following a systematic review of the literature and patient interview by a three-round Delphi process[20]. This identified 3 patient-reported outcomes (incontinence, quality of life and patient priorities) and five clinical-reported outcomes of perianal disease (activity, new abscesses or sepsis, new or recurrent fistula, unplanned surgery and fecal diversion).

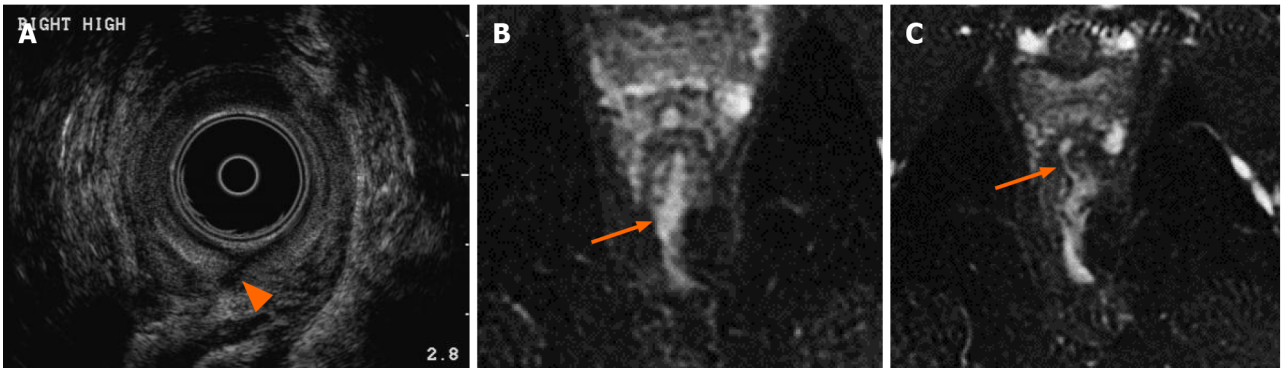

Figure 1 A 37-year-old-man with history of Crohn's disease. A: Transrectal ultrasound identifies a defect in the internal anal sphincter posteriorly (arrowhead); B: Axial T2 weighted, fat saturated image of the anal canal obtained 6 d later more clearly show a transsphincteric perianal fistula arising at 6 o'clock with a fluid filled sinus tract extending posteriorly to exit at the skin surface; C: Magnetic resonance imaging (MRI) image also demonstrates an additional transsphincteric fistula which arises at the 1 o'clock position extending anteriorly and communicating with a complex branching tract which also exited to the skin surface (not shown). MRI provides comprehensive multiplanar imaging of fistulizing disease, allowing visualization of the full extent of disease including supralevator disease and more complete classification of branching or complex fistulas. Additionally, post contrast sequences allow differentiation between fluid containing tracts from granulation tissue seen following healing.

Fistula response on MRI pelvis during follow-up was considered an optional outcome, partially related to issues with the cost and accessibility of MRI. This contrasts with the STRIDE guidelines for luminal inflammatory bowel disease, where endoscopic remission is the agreed target of medical therapy in both Crohn's disease and ulcerative colitis[21,22]. MRI provides a potential advantage over clinical evaluation for tract closure, as it has been shown that internal fistula tracts can persist despite closure of the external opening[23].

Studies evaluating MRI healing and clinical symptoms suggest that MRI healing can lag significantly behind clinical remission, with radiographic findings persisting for up to 12 months after clinical remission[24]. Additionally, many studies of long-term outcomes following treatment with infliximab based on MRI findings have not identified any MRI parameters that accurately distinguish individuals with clinical features of active disease compared to those who achieved clinical remission[25-27]. One observational study suggested that the disappearance of T2 hyperenhancement and absence of enhancement strongly correlated with clinical remission in patients who had an MRI at 12 months after treatment[28]. Many of these studies have used 1.5T MRI machines, which may provide a lower quality image than more modern machines, and there is a lack of study into newer machines, such as 3T machines and evaluation of MRI parameters. Finally, interpretation of perianal protocol MRI is experience-dependent, and outside large centers, there may not be familiarity with the correct imaging protocol and interpretation of these examinations.

Overall, this would suggest that clinical remission remains the main target in treatment of anti-TNF therapy in perianal disease; however, assessment with an MRI pelvis at baseline and during follow-up may provide further information to help guide treatment.

WHAT CAN BE DONE TO OPTIMIZE RESPONSE WHILE ON ANTI-TNF THERAPY FOR PERIANAL CROHN'S DISEASE?

Concomitant medications

Antibiotics: Three trials have evaluated the use of antibiotic therapy, primarily with ciprofloxacin, in combination with anti-TNF treatment for perianal Crohn's disease. All have shown a trend toward improved fistula response rates at 18 weeks and 24 weeks, although none of these results were statistically significant by the end of the study period[29-31]. One of these trials comparing adalimumab with ciprofloxacin to adalimumab with placebo showed an initial significant difference at week 12, with 65% achieving closure of all perianal fistulas on adalimumab with ciprofloxacin compared to 33% on adalimumab with placebo, but this difference was not sustained by the end of follow-up, despite remaining 15% higher in the adalimumab with ciprofloxacin group (62% *vs* 47%, respectively). These studies may have been underpowered to show a significant difference between the groups, and a meta-

analysis suggested that the induction of fistula response (relative risk, 1.58) and remission (relative risk, 1.94) is significantly superior with antibiotics in combination with infliximab compared to anti-TNF therapy alone[32]. The use of antibiotics in this setting, therefore, has been advised by experts, particularly during initial treatment of perianal disease with anti-TNF therapy[33,34].

Immunomodulator therapy: There have not been any dedicated randomized trials specifically comparing use of anti-TNF therapy in combination with immunomodulator therapy to anti-TNF monotherapy. A secondary analysis of two of the placebo-controlled randomized studies comparing infliximab and placebo for perianal Crohn's disease compared anti-TNF therapy in combination with immunomodulators and anti-TNF monotherapy, and did not show a difference in fistula outcomes with induction or maintenance treatment[12,35]. Similar findings were also noted in observational studies comparing combination therapy to infliximab monotherapy[36,37]. It should be noted, however, that patients in these studies had previously failed to achieve a response with immunomodulator therapy prior to initiation of anti-TNF therapy, and some observational studies have shown a significantly higher rate of fistula closure amongst patients on combination therapy compared to anti-TNF monotherapy[38]. None of the aforementioned studies evaluated the use of anti-TNF therapeutic drug monitoring, so it is not clear whether any benefit is related to the effect of the immunomodulator on anti-TNF levels or independent of this. Given the known effects of immunomodulators of reducing immunogenicity and therefore increasing levels of infliximab, and the fact that higher anti-TNF drug levels have been associated with greater response in perianal Crohn's disease (see the below section on 'Therapeutic drug monitoring'), serious consideration should be given to commencing an immunomodulator with anti-TNF therapy, particularly if proactive therapeutic drug monitoring is not being utilized.

Therapeutic drug monitoring

Multiple retrospective and observational studies have identified an association between higher infliximab drug levels and a greater rate of fistula response, healing and closure[39-43]. While the cut-off infliximab level has varied between studies, possibly related to the assay used and end points assessed, it appears that the target level is higher than what is conventionally used to control luminal Crohn's disease (Table 1). Davidov *et al*[44] performed infliximab levels during induction therapy for patients with perianal Crohn's disease and found that those who had a clinical response to treatment by week 14 had significantly higher median infliximab drug levels beginning at week 2 (20 μg/mL *vs* 5.6 μg/mL), and these remained higher than non-responders at weeks 6 (13.3 μg/mL *vs* 2.55 μg/mL) and 14 (4.1 μg/mL *vs* 0.14 μg/mL). Yarur *et al*[39] similarly found significantly higher trough infliximab levels in a cross-sectional study of individuals with perianal Crohn's disease on long-term infliximab who achieved fistula healing compared to those who did not achieve healing (median, 15.8 mcg/mL *vs* 4.4 mcg/mL, $P < 0.001$). This study also found that the odds of achieving fistula healing were over 8 times greater in individuals who underwent dose escalation of infliximab. Intuitively this would suggest that monitoring anti-TNF drug levels proactively and performing dose adjustments in individuals with lower levels may improve fistula healing rates, although this has not been prospectively evaluated.

Duration of anti-TNF therapy and discontinuation

De-escalation of medical therapy in inflammatory bowel disease involves the deliberate reduction in dose or cessation of a treatment once the treatment target has been achieved. A key component of de-escalation of therapy is establishing a treatment target that has good correlation with better long-term outcomes. In luminal Crohn's disease, it has been established that endoscopic remission correlates better with the long-term clinical course of inflammatory bowel disease than symptomatic remission [45]. However, given that treatment of perianal disease remains primarily targeted at symptom-based remission, de-escalation of therapy may be more difficult to complete successfully.

The ACCENT II study evaluated the need for ongoing infliximab therapy in patients with perianal Crohn's disease by comparing the proportion of individuals who lost response to maintenance therapy with either placebo or ongoing infliximab in all individuals who achieved a clinical response to infliximab induction therapy[35]. After 52 wk, 42% of patients had lost response in the infliximab maintenance group compared to 62% in the placebo group ($P < 0.001$). Other retrospective studies have also found that over half of patients who cease anti-TNF therapy will have a clinical

Table 1 Table of trials evaluating ideal cut off value for infliximab and adalimumab concentrations

Ref.	Population (adults or children)	Number	Study design	Follow up or time on therapy	Outcomes	Median level	Median level
Trial: Infliximab							
Plevris *et al* [43]	Adult	29	Retrospective single center cross sectional	2.6 yr	Fistula healing; Fistula closure	8.1; 8.2	3.2; 3.2
Strik *et al*[40]	Adult	47	Retrospective single centercross sectional	3.5 yr	Fistula closure	6.0	2.3
Davidov *et al* [44]	Adult	36	Retrospective observational two centers	Week 2; Week 6; Week 14	Decrease or cessation of fistula drainage at week 14	20; 13.3; 4.1	5.6; 2.55; 0.14
Zhu *et al*[69]	Adult	157	Retrospective single center	Week 30; Week 78; Week 116	Radiological remission (absence of high-signal tracks on fat-saturated T2-weighted sequences)	3.5; 2.85; 2.84	1.9; 1.63; 0.7
El-Matary *et al*[42]	Pediatric	85	Prospective observational 12 centers	Week 14	Clinical fistula healing at week 24	12.7	5.4
Yarur *et al* [39]	Adult	117	Retrospective, cross sectional, 2 centers	29 wk	Fistula healing	15.8	4.4
Trial: Adalimumab							
Plevris *et al* [43]	Adult	35	Retrospective single center cross sectional	1.7 yr	Fistula healing; Fistula closure	14.8; 12.6	5.7; 2.7
Strik *et al*[40]	Adult	19	Retrospective single center cross sectional	3.5 yr	Fistula closure	7.4	4.8
Ruemmele *et al*[41]	Pediatric	36	Randomized control trial	Week 16; Week 52	Clinical fistula closure	7.4; 7.5	6.4; 5.6

relapse with long-term follow-up, so stopping treatment either due to clinical remission or for other reasons is associated with a high risk of relapse[46-48].

Radiological healing is a more stringent treatment target in perianal Crohn's disease, and whether anti-TNF therapy can be stopped after this end point is achieved has not been well studied. A prospective observational study identified 12 patients who were treated with infliximab alone or in combination with a thiopurine who achieved radiological healing[24]. Amongst this group, 5 remained on infliximab therapy and 7 stopped treatments either due to intolerance, treatment de-escalation or switched therapies. There was a trend toward greater rates of radiological healing amongst individuals who remained on infliximab as all maintained radiological remission, while 3/7 in the group that stopped infliximab maintained radiological remission (P = 0.08). Another observational study found that 6/9 (67%) of patients who had achieved radiological healing and stopped maintenance anti-TNF therapy had fistula recurrence[49]. This data would support the use of ongoing anti-TNF therapy in patients who achieve clinical remission of perianal fistulae.

WHAT OTHER THERAPIES CAN BE USED FOLLOWING ANTI-TNF FAILURE?

Vedolizumab

No dedicated randomized controlled trials have assessed the efficacy of vedolizumab for perianal Crohn's disease, and clinical data have shown limited benefit. A post hoc analysis of the GEMINI 2 study compared the efficacy of maintenance vedolizumab to placebo in achieving fistula closure at weeks 14 and 52 following therapy with vedolizumab amongst patients with at least 1 externally draining fistula related to Crohn's disease[50]. Over 40% of patients in each group had previously been treated with anti-TNF therapy. The study identified a numerical difference in fistula closure rates in favor of vedolizumab at week 14 (28% *vs* 11%) and 52 (31% *vs* 11%), although these did not reach statistical significance, and no difference was noted between maintenance therapy given every 4 wk or 8 wk. The ENTERPRISE study was a

randomized trial comparing two intravenous regimens of vedolizumab for treatment of perianal Crohn's disease, with 78% of patients having previously failed anti-TNF therapy[51]. Patients either received standard induction vedolizumab of 300 mg at weeks 0, 2 and 6 then at weeks 14 and 22, while the other group received the same regimen plus a week 10 dose. There was no placebo group in the study and 92% of patients had a seton inserted at baseline. They found that by week 30, 54% of the group had a clinical response to treatment, while 43% had complete closure of fistulae and there was no significant difference between the groups. A nationwide cohort study of 151 patients with perianal Crohn's disease (99% of patients having previously been treated with at least one anti-TNF) who were treated with vedolizumab showed that 23% of patients achieved clinical success (no draining fistula at clinical examination) after 6 mo of treatment, while 67% of patients stopped vedolizumab by 30 wk of treatment due to uncontrolled perianal or luminal disease[52]. Additionally, 31% of patients with perianal disease who had no clinical symptoms at the time of initiation of vedolizumab developed symptoms after commencing therapy. Concomitant immunomodulator therapy was used in 44% of patients in this cohort and this was not a predictor of the success of therapy. Based on these data it appears that there is insufficient evidence to support the widespread use of vedolizumab following anti-TNF failure in perianal Crohn's disease, and further dedicated studies are needed.

Ustekinumab

Available data have provided some support for the use of ustekinumab for perianal disease amongst patients who have trialed or failed anti-TNF therapy. A post hoc analysis of the combined results on fistula healing from the large placebo-controlled trials for ustekinumab in Crohn's disease found that there was a trend toward higher rates of resolution of fistula symptoms by week 8 of ustekinumab therapy compared to placebo (25% *vs* 14%) which had increased to 80% *vs* 46% by week 44[53]. Numbers in the latter analysis were small, with just 26 patients in both groups, and the results were not statistically significant. These trials included a combination of anti-TNF-naïve and anti-TNF-experienced patients, and the results do not distinguish between the groups. A Dutch Nationwide study in which 99% of patients had prior exposure to at least one anti-TNF therapy found that 36% of individuals with perianal fistula at initiation of ustekinumab achieved complete clinical resolution by 24 wk[54]. Further retrospective studies into the use of ustekinumab for perianal Crohn's disease were combined with the aforementioned results in a meta-analysis which found a 56% response rate and 17% remission rate after 52 wk of therapy[55]. Moderate heterogeneity was noted. It appeared that the efficacy of ustekinumab increased between week 8 and week 52. For individuals who are not responding to initial ustekinumab, the use of dose intensification of therapy can result in a clinical response in perianal disease, with one observational study noting 12/24 patients (50%) when escalated to four or six weekly therapy[56]. The limited data available on the use of ustekinumab levels in perianal Crohn's disease do not show an association between serum levels during induction nor maintenance therapy and fistula response at 44 wk[57]. A major limitation of these observational studies is the lack of a comparator being utilized, so while these results suggest ustekinumab may be beneficial in individuals who do not respond to anti-TNF therapy, the size of this effect is not known.

Mesenchymal stem cell therapy

While the exact mechanism that leads to the efficacy of mesenchymal stem cells in the treatment of perianal Crohn's disease is not known, it likely relates to their ability control the local inflammatory response and allow for fistula healing[58]. A placebo-controlled randomized trial found a single dose (120 million cells) of intralesional injection of adipose derived allogeneic cells to the fistula tract in patients with perianal Crohn's disease who were refractory to medical therapy (79% treated with anti-TNF therapy in past 6 mo) achieved combined clinical and radiographic remission in 56% of patients compared to 39% in the placebo group after 12 mo[10,59]. Further studies evaluating the use of both autologous adipose-derived mesenchymal stem cells and bone marrow-derived mesenchymal stem cells have also shown efficacy of these therapies[11,60-62]. While questions remain regarding the optimal dosing and treatment protocol to use, the results suggest treatment to be efficacious and safe even amongst individuals who are not responding to anti-TNF therapy, so this will likely remain an important therapeutic option to consider when it widely available.

Temporary fecal diversion

Reports of the efficacy of a temporary diverting stoma in the pre-biologic era

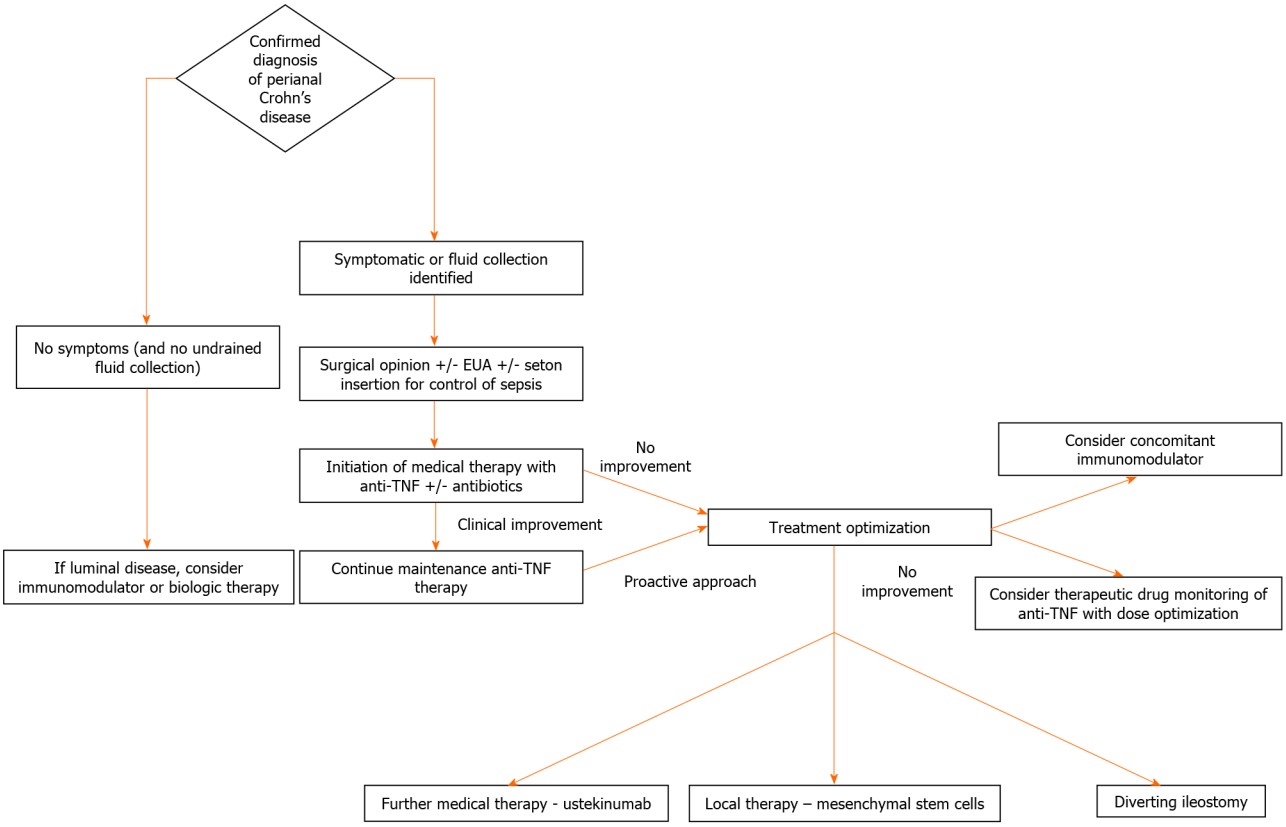

Figure 2 A suggested approach to treatment in perianal Crohn's disease. Anti-TNF: Anti-tumor necrosis factor; EUA: Examination under anesthesia.

suggested it was highly efficacious, with response rates reported to occur in over 80% of individuals in the short term[63,64] and a meta-analysis found response rates in 3 mo to 6 mo in 64% of individuals[65]. However, reports of the use of defunctioning stoma in individuals after failing biologic therapy has shown a lower response rate, with cohort studies suggesting response rates of 46%[66,67]. Rates of successful restoration of bowel continuity also remain low at 18%, and the use of biologic therapy following diverting therapy does not appear to improve the rate of stomal reversal[65,68]. This suggests that while defunctioning surgery remains an option following failure of anti-TNF therapy, the chances of restoration of bowel continuity remain low.

CONCLUSION

Anti-TNF therapy remains the most established therapy for the treatment of perianal Crohn's disease. Emerging evidence would support its early use in treatment, in combination with surgical intervention, to try to minimize complications from perianal disease (Figure 2).

Antibiotics should be considered during induction anti-TNF therapy, but their benefits beyond 24 weeks are not known. While on anti-TNF therapy the use of therapeutic drug monitoring and optimization of anti-TNF levels may improve fistula response rates, but it is likely that higher anti-TNF drug levels are required than are used for the treatment of luminal Crohn's disease. The use of combination therapy with an immunomodulator may be beneficial, particularly in individuals who have not previously failed immunomodulator therapy, although the additional benefit of immunomodulator therapy beyond improving immunogenicity of anti-TNF therapy is not known.

In individuals who fail to respond to anti-TNF therapy for perianal Crohn's disease, ustekinumab may allow for healing of fistula and dose interval shortening of therapy may be of benefit in individuals who are not responding to 8-weekly therapy.

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