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Treatment of Fibrostenotic and Fistulizing Crohn's Disease

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Key Words
Crohn's disease · Stricture · Perianal fistulas

Abstract
The majority of Crohn's disease patients will develop a complicated disease course over time which is characterized by the occurrence of stricturing and penetrating disease. Penetrating disease comprises internal fistulas (e.g. enteroenteric) and perianal disease. A complicated disease course may be associated with considerable morbidity and professional and personal disabilities. Treatment options for fibrostenotic Crohn's disease comprise endoscopic balloon dilation, stricturoplasties and surgical resection. Treatment of symptomatic perianal fistulizing disease is based on antibiotics, immunomodulators and anti-TNF drugs. Surgical measures include fistula drainage by means of setons, temporary ileostomy or a proctectomy. The presence of internal fistulas often necessitates surgical measures. A close collaboration between the gastroenterologist and the surgeon is mandatory to solve these interdisciplinary challenges.

Introduction

Crohn's disease (CD) manifests with three distinct behavioural forms, namely an inflammatory, a stenosing and a penetrating phenotype [1]. At CD diagnosis, the majority of patients present with an inflammatory phenotype, whereas the stenosing and fistulizing phenotype develop over time. About 20–30% of patients present at diagnosis with perianal lesions and 15–20% have or have had a fistula. The cumulative risk for perianal involvement increases to 50% over time [1]. Schwartz et al. [2] reported a fistula occurrence of 35% over time. Of these fistulas, 54% were perianal, 24% were enteroenteric, 9% were rectovaginal and 13% involved other locations, i.e. enterocutaneous, enterovesical and intraabdominal fistulas. They found a cumulative fistula incidence of 33 and 50% at 10 and 20 years after CD diagnosis, respectively [2]. Fistulas can manifest with persistent anal pain, painful defecation and as perianal openings with purulent discharge. Perianal fistulas may also be the initial manifestation of CD [3]. The fistulous openings are most commonly located in the perianal skin, but can also be found in the scrotum, vulva or groin.

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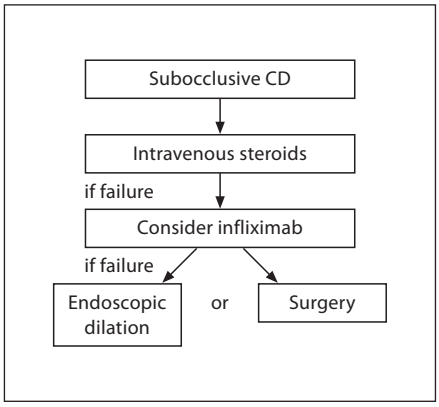

Fig. 1. An algorithm for the therapy of fibrostenotic CD.

Perianal fistulas can be classified based upon their anatomic extensions into simple and complex fistulas. Simple fistulas are located in the dentate line, have a single external opening, are not painful and have no evidence of rectovaginal fistula or anorectal stricture. Complex fistulas are located above the dentate line, may have multiple openings, show evidence of an abscess and may be associated with pain, with the presence of a rectovaginal fistula, anorectal stricture or active rectal disease at endoscopy [4]. The risk of fistula development is higher in patients with colonic CD, in particular in those with rectal involvement, compared to patients without colorectal disease [1]. The diagnosis of perianal fistulas relies on clinical examination and imaging where mostly a pelvic MRI is used [5]. Perianal fistulas may be evaluated according to the Perianal Disease Activity Index [6], which evaluates five categories (discharge, pain, restriction of sexual activity, type of perianal disease and degree of induration) or according to the finger compression technique, which evaluates a reduction of 50% in the number of draining fistulas observed on two or more consecutive visits as assessed by the study investigator using gentle finger compression [7]. Currently, there is no widely accepted and validated scoring system for fistulas in CD. The definition of 'response to therapy' varies from study to study. Caution should be executed regarding which definitions have been used for fistula assessment.

Nonperianal fistulas (such as enteroenteric, enterovesical or enterocutaneous fistulas) are diagnosed clinically and also by using imaging techniques such as bowel MRI [5]. Data on the treatment strategies of nonperianal fistulas are limited. Fibrostenotic CD usually presents with obstructive symptoms. Strictures are mostly located in the ileocecal region [1].Symptoms due to strictures may be aggravated by a superimposed edema due to active inflammation. Therefore, a trial of short duration with steroids may be performed to evaluate whether the obstructive symptoms improve [8]. For the assessment of therapeutic responses of treated fistulas, it should be kept in mind that the natural history of fistulas is unpredictable and that they therefore sometimes also close under placebo treatment [9].

This review focuses on treatment strategies for fibrostenotic and fistulizing CD.

Therapy of Fibrostenotic Crohn's Disease

Therapy options for treating fibrostenotic CD include anti-inflammatory medication, endoscopic balloon dilation and surgery. A therapeutic algorithm is presented in figure 1.

Anti-inflammatory Medication

In patients with evidence of obstructive symptoms, a short-duration trial with steroids may be performed first, in order to evaluate if these symptoms improve [8]. A persistence of symptoms, despite intravenous steroids, is an indication of fibrotic strictures without any relevant edema caused by acute inflammation. Pre-existing bowel stenoses were considered as representing a contraindication for treatment with infliximab when this drug was approved for CD treatment. However, patients with mixed strictures (stenotic and inflammatory) may benefit from infliximab therapy [10, 11]. Holtmann et al. [12] retrospectively evaluated 21 CD patients treated with infliximab, 11 of whom had an inflammatory stenosis. Nine of these responded well to infliximab and became asymptomatic for a considerable period of time. A multivariate analysis from the TREAT registry and the ACCENT I trial demonstrated that infliximab treatment did not increase the likelihood of stenosis [13].

Endoscopic Balloon Dilation

Endoscopic dilation for Crohn's strictures offers the advantage of a nonsurgical procedure. Hassan et al., via a meta-analysis of 13 studies, evaluated a total of 347 CD patients who had undergone balloon dilation for mostly postsurgical strictures [14]. The dilations were technically successful in 86% of the cases. Long-term clinical efficacy was achieved in 58% of patients for a mean follow-up of 33 months with a major complication rate of 2%. A stricture length of ≤ 4 cm was associated with a surgery-

free outcome (OR 4.01, $p < 0.028$). We can conclude from this review that endoscopic balloon dilation represents a valuable option in CD patients with short strictures.

Strictureplasty and Resective Surgery

Strictureplasty increases the bowel diameter without any resection. The procedure is technically feasible for short stenoses. It yields results comparable with bowel resections regarding the improvement of obstructive symptoms, the reoperation rate and the time interval to symptom recurrence [15]. Fearnhead et al. [16] analyzed 479 strictureplasties performed in 100 CD patients during 159 operations. The reoperation rate was 52% at a mean of 40.2 months after a first strictureplasty and 56% at 26.1 months after a second strictureplasty. The major risk factor for reoperation was a young age ($p < 0.001$).

Limited surgery for CD is able to effectively relieve obstructive symptoms in stenotic CD. Wide resection margins do not have any effect on recurrence [17]. Repetitive resective surgery should be avoided to reduce the risk for short bowel syndrome.

Therapy of Perianal Fistulizing Crohn's Disease

The treatment modalities for perianal fistulizing disease include surgical and medical therapies. Asymptomatic simple perianal fistulas do not require any specific treatment [5]. Therapeutic options for symptomatic simple perianal fistulas consist of noncutting seton or fistulotomy and adding antibiotics such as metronidazole or ciprofloxacine [5]. Surgical treatment is generally recommended for complex perianal disease and includes abscess drainage and seton placement. Fistulectomy and fistulotomy should be conducted with caution given the risks of fecal incontinence [5]. For severe perianal disease refractory to medical therapy, a diverting stoma or a proctectomy may be necessary.

The following medical treatment options are applied for complex perianal fistulas: antibiotics, azathioprine/6-mercaptopurine, methotrexate, anti-TNF therapy (infliximab, adalimumab or certolizumab pegol), ciclosporin A and tacrolimus.

Antibiotics

Evidence for the use of antibiotics in complex perianal disease is based on mainly small trials. Antibiotics are effective for improvement of symptoms, but rarely induce fistula healing. The recurrence rate at withdrawal is high. Metronidazole is widely used for fistula treatments [18, 19]. A response can be expected after 6–8 weeks of treatment. Metronidazole was associated with perianal fistula closure in up to 83% in an open-label case series [18]. Several side effects such as nausea, a metallic taste in the mouth and peripheral neuropathy limit its use for long-term treatment [19]. Ciprofloxacin has only been evaluated for perianal CD treatment in uncontrolled, small studies [20, 21]. Long-term use of ciprofloxacin may be associated with spontaneous Achilles tendon rupture. Ciprofloxacin combined with infliximab was evaluated for the treatment of perianal fistulizing CD in a double-blind placebo-controlled study [22]. All patients were on infliximab and were randomized to receive either ciprofloxacin or placebo. Patients also treated with ciprofloxacin responded more favorably than those on placebo therapy (OR 2.37, $p = 0.07$), which suggests that ciprofloxacin in combination with infliximab may be more effective than infliximab on its own.

Azathioprine/6-Mercaptopurine

There are no randomized controlled trials that have assessed the effect of azathioprine or 6-mercaptopurine on the closure rate of perianal fistulas as a primary end point. A meta-analysis of 5 randomized controlled trials where perianal fistula closure was assessed as secondary outcome indicates the efficacy of these drugs for closing and maintaining the closure of perianal fistulas (OR 4.44, CI 1.50–13.20) [23].

Methotrexate

The evidence for using methotrexate in perianal CD is limited. In a retrospective study assessing 16 patients with perianal fistulizing disease and failure or intolerance to 6-mercaptopurine therapy, 4 (25%) experienced complete fistula closure and 5 (31%) experienced a partial closure [24]. We conclude that, in CD patients who are intolerant or nonresponsive to azathioprine or 6-mercaptopurine therapy, methotrexate may be used for the treatment of perianal fistulizing disease.

Infliximab

In randomized controlled trials, the efficacy of infliximab for the induction and maintenance of perianal fistulas was demonstrated. Treatment of simple and complex perianal fistulas with 5mg/kg at weeks 0, 2 and 6 induced complete fistula closure (defined as cessation of all drainage at two visits 1 month apart) in 17/31 (55%) of patients [25]. In the ACCENT II trial, an initial response rate of

69% (195/306) was documented at week 14 and responders were randomized to receive 5 mg/kg or placebo every 8 weeks [26]. At week 54, 33/91 (36%) of patients on infliximab experienced complete fistula closure compared to 19/98 (19%) on placebo ($p = 0.009$). Response, defined as >50% fistula closure on clinical assessment, was documented in 46% of patients on infliximab compared to 23% on placebo ($p = 0.01$) [26].

Adalimumab

In the placebo-controlled CHARM trial (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance), 117 of 778 CD patients had actively draining perianal fistulas [27, 28]. Patients initially received 80 mg of adalimumab, then 40 mg 2 weeks' later, followed by 40 mg every 2 weeks, 40 mg weekly or placebo. Patients with draining fistulas were evaluated for healing at week 26 and at week 56 as a secondary endpoint. Thirty percent (21/70) of all randomized patients on active adalimumab maintenance treatment had complete healing at both time points, compared with 13% (6/47) on placebo maintenance ($p < 0.04$). Of all the patients with healed fistulas at week 56, 90% (28/31) maintained healing for 1 further year of open-label adalimumab therapy [28].

Certolizumab Pegol

Certolizumab pegol was evaluated in patients with CD via 2 large studies, PRECiSE 1 and 2 (Pegylated Antibody Fragment Evaluation in Crohn's Disease Safety and Efficacy) [29, 30]. In both studies, only a small number of the patients included suffered from fistulizing disease and the percentage of patients with complete fistula healing was not statistically different at week 26 and week 20, respectively, between the placebo group and the certolizumab-pegol-treatment group. The two studies were not powered to demonstrate a difference in perianal fistula healing. An open-label phase-IV study in 60 CD patients demonstrated a complete perianal fistula closure of 36% at week 6 and of 55% at week 26 [31].

Cyclosporine and Oral Tacrolimus

Evidence of these drugs for the treatment of perianal CD comes from uncontrolled case series with a limited patient number. Intravenous cyclosporine and oral tacrolimus both improve or heal a substantial proportion of patients short-term, but they often relapse upon cessation of the drug [32, 33]. The side effect profile of both drugs limits the long-term use for treatment of fistulizing CD [5].

Therapy of Non-Perianal Fistulizing Crohn's Disease

There is a lack of randomized trials evaluating nonperianal fistulizing CD medical treatment. The management of nonperianal fistulizing CD remains an interdisciplinary challenge and involves the gastroenterologist, radiologist and surgeon. Treatment options include medication (see above) and surgical procedures [5]. An in-depth review of nonperianal fistulizing CD is out of the focus of this review and we therefore refer to comprehensive guidelines [5].

Conclusion

The majority of CD patients will experience complications in the form of strictures and/or fistulas (perianal or non-perianal). Treatment options for stricturing disease involve anti-inflammatory therapy, balloon dilation and surgical measures. Perianal fistulizing disease can be divided into simple and complex. Fistulas and abscesses should be drained before initiating anti-inflammatory therapy. Antibiotics offer symptom relief for patients with perianal disease, but have no role as a maintenance regimen. Immunomudulators such as azathioprine and 6-mercaptopuriine have a proven role in inducing and maintaining fistula closure. The therapeutic efficacy of methotrexate in perianal disease is limited but it can be used in patients with an intolerance or lack of response to azathioprine/6-mercaptopurine. Infliximab and adalimumab have shown in randomized controlled trials their efficacy in induction and maintenance of fistula closure. Certolizumab pegol has shown efficacy in fistula closure in a phase IV study. Stricturing and fistulizing disease have to be approached in an interdisciplinary way involving the gastroenterologist, the surgeon, and the radiologist.

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Disclosure Statement

The authors declare no conflict of interest.

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