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Improving the outcome of fistulising Crohn's disease

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A B S T R A C T

Fistulas are a frequent manifestation of Crohn's disease (CD) and can result in considerable morbidity. Approximately 35% of all patients with CD will experience one fistula episode during their disease course of which 54% is perianal. The major symptoms of patients with perianal fistulas are constant anal pain, the formation of painful swellings around the anus and continuous discharge of pus and/or blood from the external fistula opening. The exact aetiology of perianal fistulas in CD patients remains unclear, but it is thought that a penetrating ulcer in the rectal mucosa caused by active CD forms an abnormal passage between the epithelial lining of the rectum and the perianal skin. Genetic, microbiological and immunological factors seem to play important roles in this process. Although the incidence of perianal fistulas in patients with CD is quite high, an effective treatment is not yet

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discovered. In this review all available medical and surgical therapies are discussed and new treatment options and research targets will be highlighted.

Introduction

Fistulas in Crohn's disease (CD) are a major problem which can result in considerable morbidity. Approximately 35% of all CD patients have at least one fistula episode. A quarter of the fistulas is between two parts of intestine, 9% is rectovaginal and 13% is different, including fistulas between the intestine and bladder and around a stoma [1]. In case of an enterovesical fistula there may be recurrent polymicrobial urinary tract infections, pneumaturia and faecaluria. When a rectovaginal fistula develops, dyspareunia, malodorous vaginal discharge and recurring episodes of vaginitis can occur. Perianal fistulas are the most common type of fistulas in fistulising CD. The cumulative incidence of perianal fistulas was estimated at 23%–26% after 20 years of CD [1,2]. Patients with perianal fistulas can present with symptoms such as constant anal pain or pain after defecation, (painful) swelling around the anus, continuous (malodourous) discharge of pus and/or blood from the external opening with skin irritation around the anus, fever and even incontinence [3]. In 20–45% of the CD patients a perianal fistula developed before or at the time of diagnosis CD [1,2]. Patients with colonic and active rectal disease have more frequently perianal fistulas compared to patients with isolated ileal or ileocolonic disease [1,2,4–6]. Male gender, age at diagnosis of CD and smoking are other risk factors although data are conflicting [1,2,5,7–9]. The formation of perianal fistulas in CD is based on the presence of a penetrating ulcer in the rectal or anal mucosa resulting in an abnormal granulating connection between the epithelial lining of the rectum or anal canal and the perianal skin [10,11]. However, most perianal fistulas are cryptoglandular fistulas (90%) and are not associated with CD. They originate from the intersphincteric anal glands due to a local infection with abscess formation [12]. Normally the internal sphincter is a barrier for bacterial overgrowth, only chronic infection, CD inflammation or local

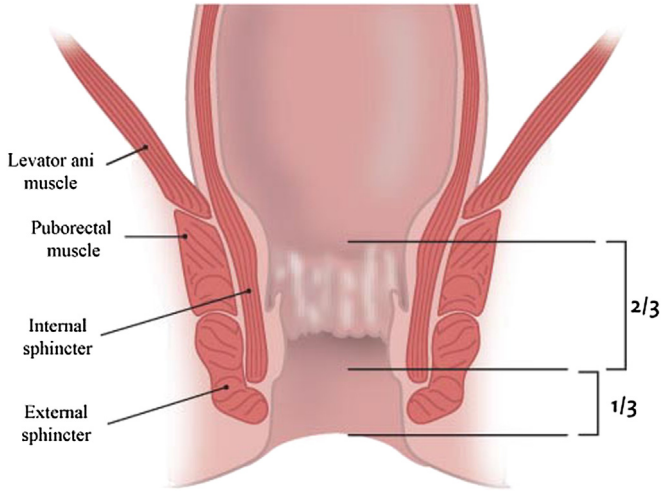

Fig. 1. Anatomy of the muscles surrounding the rectum and anal canal. A fistula tract through the lower third of the external muscle is classified as a low perianal fistula; fistulas in the two-thirds above as high perianal fistulas. Figure reproduced with permission from Bemelman from van Koperen et al [93].

trauma can cause abscesses beyond this barrier in the intersphincteric space. When such an abscess increases it will usually drain in two ways: it can either drain through the intersphincteric space downwards to form an intersphincteric fistula erupting into the perianal skin or it can overcome the external sphincteric plane into the ischiorectal fossa resulting in a transsphincteric perianal fistula. In

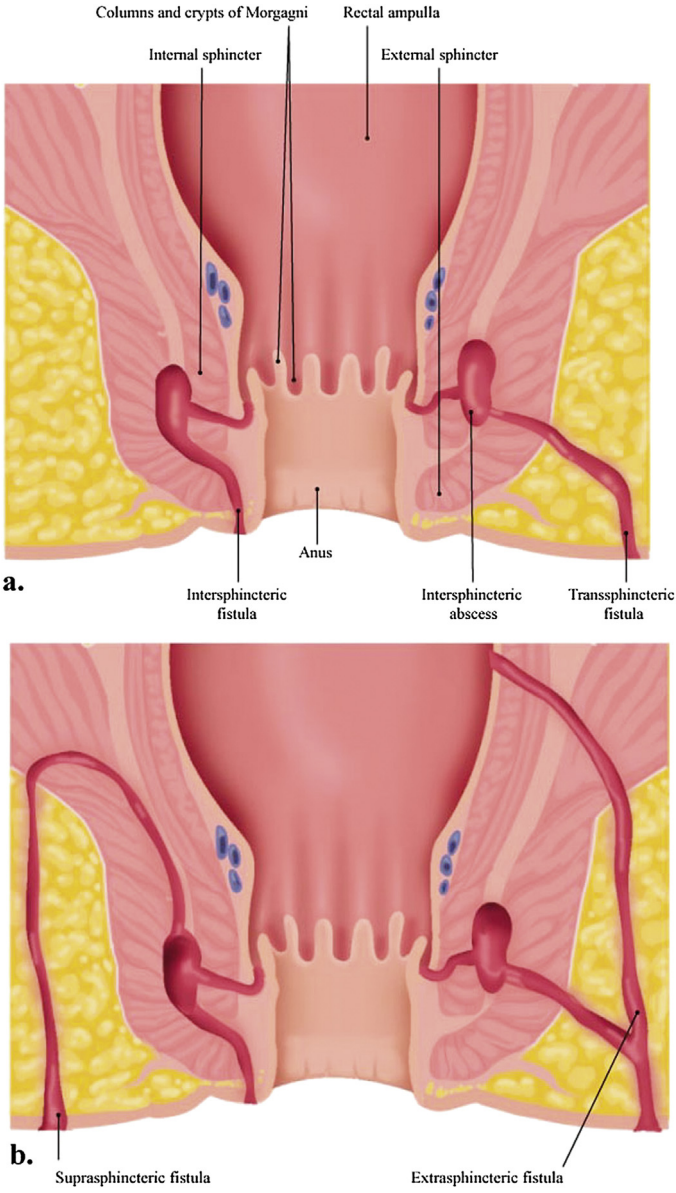

Fig. 2. Parks classification of perianal fistulas. (a) An intersphincteric fistula situated between the internal and external sphincter and a transsphincteric fistula passing the internal and external sphincter into the ischiorectal fossa. (b) A suprasphincteric fistula passing through the external sphincter above the puborectalis muscle into the ischiorectal fossa and an extrasphincteric fistula with its origin above the puborectalis draining through the pelvic floor into the ischorectal fossa without passing the internal or external sphincter. Figure reproduced with permission from Schouten from Schouten et al [94].

CD these abscesses are often a complex delta of channels and patients might present with large or multiple abscesses. The exact aetiology of perianal fistulising CD remains unclear, however genetic, microbiological and immunological factors seem to play important roles. The risk haplotype of the carnitine/organic cation transporter (OCTN) on the IBD5 locus (5q31) is associated with penetrating and perianal CD due to altered bacteria killing resulting in inflammation [13]. Furthermore, diminished clearance of intracellular pathogens by autophagy caused by a specific polymorphism in the immunity-related GTPase family M (IRGM) gives an increased risk of penetrating and perianal CD [14]. It is hypothesized that microbiota also contribute to the development of perianal fistulas as faecal diversion leads to long-term improvement [15]. Especially gram-positive microorganisms are present in CD perianal fistulas [16]. The likelihood of spontaneous healing of perianal fistulas is very low as the rectum, where the luminal opening of perianal fistulas in CD is most frequently located, functions as a reservoir for faeces that is pushed into the luminal opening of the fistula resulting in a continuous contamination. More importantly, epithelialization of the fistula tract in patients with CD hinders fistula closing. Although a range of potent drugs and advanced surgical techniques are available nowadays, the treatment of perianal fistulising CD remains challenging. In this review both classical and future treatments for perianal CD will be discussed.

Anatomy (Fig. 1)

The anal canal is approximately 2–4 cm long and is closely related to both the internal and external sphincter that both play an important role in remaining faecal continence. The internal sphincter (inner muscular layer) is a continuation of the circular smooth muscular layer of the rectum and becomes thicker at the anal canal. The external sphincter is formed from the pelvic floor musculature. Because the external sphincter is longer than the internal sphincter it covers the internal sphincter to the anoderm. The surface of the anal canal is formed by the mucosa of the rectum with columnar epithelium (endoderm) and the mucosa of the skin with squamous epithelium (ectoderm). The junction of these two surfaces is the linea dentata or pectinate line. Above the pectinate line the mucosa is folded into columns: the columns and crypts of Morgagni with ducts to the anal glands. These anal glands penetrate into the intersphincteric space.

Classification

Nowadays, the relative simple Parks classification [17] identifying four types of perianal fistulas (intersphincteric, transsphincteric (Fig. 2(a)), suprasphincteric and extrasphincteric (Fig. 2(b)) is often used. This Parks classification is also useful for CD, although more (complicated) tracts can occur in a CD patient. Furthermore, this system does not include other perianal manifestations of CD (e.g. abscesses or strictures). In clinical practice the 'simple' or 'complex' classification combining physical inspection of the perianal area and endoscopy to determine rectal inflammation, is mostly used [6,11]. A simple fistula has its origin below the pectinate line (superficial, low intersphincteric or low transsphincteric) and has a single external opening without evidence of a perianal abscess, a rectovaginal fistula or an anorectal stricture. A complex fistula is high intersphincteric, high transsphincteric, extrasphincteric or suprasphincteric and may have multiple external openings. They may be associated with a rectovaginal fistula, an anorectal stricture, active rectal disease at endoscopy and pain or fluctuation suggesting a perianal abscess.

Diagnosis

Knowledge about the exact route and internal opening of the fistula, its relation to the sphincters and the presence of abscesses, is crucial in the management of perianal fistulising CD. Inspection of the perianal area is the first step in this process. The fistula disease activity can be quantified with the Perianal Disease Activity Index (PDAI) [18] and comprises five categories: discharge, pain/restriction activities, restriction of sexual activity, type of perianal disease and the degree of induration (all 0–4 points). Pelvic magnetic resonance imaging (MRI) (Fig. 3) is accurate in determining the exact route of the fistula, differentiating between a fibrotic and septic fistula and locating abscesses [19–22]. Introducing an endoanal coil receiver results in more detailed images of the location of the internal opening,

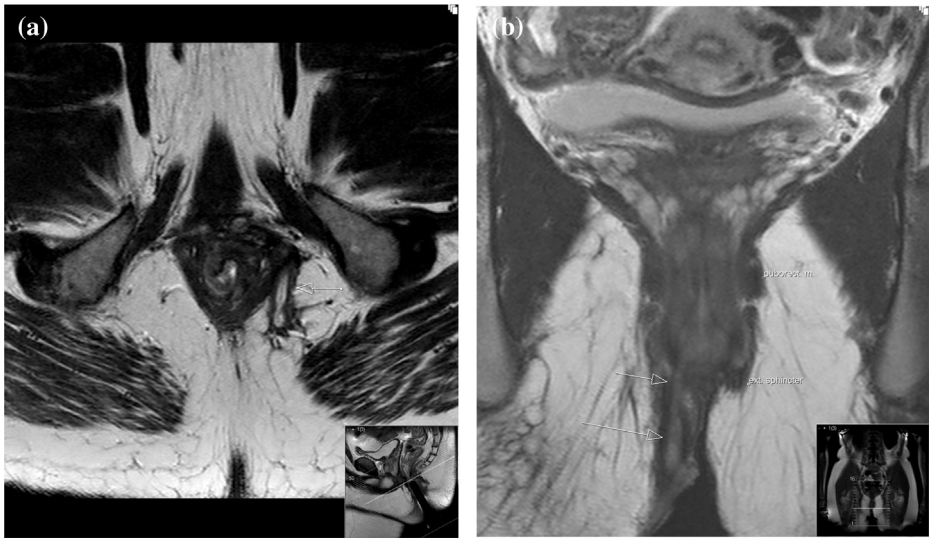

Fig. 3. Pelvic magnetic resonance imaging (MRI) of a perianal fistula. (a) Transversal image of a perianal fistula (arrow) after introduction of an endoanal coil receiver and (b) a coronal image of a perianal fistula (arrows). The fistula tract shows a high signal intensity indicating active disease.

the extent of the fistula tract and its relation with the sphincters [23,24]. Anorectal endoscopic ultrasound (EUS) requires expertise, but can be equivalent to pelvic MRI and is less expensive and time consuming [25,26]. Examination under anaesthesia (EUA) has the advantage of the possibility of concomitant drainage of abscesses and placement of non-cutting setons. The presence of related abnormalities is not detectable with digital examination (e.g. high abscesses and sinuses). In addition, MRI predicts patient outcome better than solely EUA [27,28]. The random combination of two of three methods (MRI, EUS and EUA) resulted in a 100% correct classification of perianal fistulising CD [29].

Description of perianal fistulas with older methods such as fistulography and computerized tomography (CT) is obsolete, because using these techniques it is not possible to distinguish between a fibrotic and septic fistula. Furthermore, small secondary tracts may not be visible with fistulography.

Independent of the diagnostic method used, proctosigmoidoscopy should be performed to assess whether the rectum and/or sigmoid is inflamed since active inflammation influences therapy choice and outcome.

Treatment

Treatment of perianal fistula is often indicated. Apart from the inconvenience of discharge from an untreated fistula, development of abscesses, sepsis, incontinence and carcinoma [30,31] have been described. Although a range of medical and surgical options is available nowadays, the treatment of perianal fistulas is still challenging. Achieving complete closure of the fistula tract is a long process with in many cases multiple relapses. Spontaneous closure of complex fistula in CD is rare, though it has been reported that a simple transsphincteric fistula has a spontaneous closure rate up to 50% [32]. Nevertheless the chance of recurrence is up to 60% after two years [33].

Classical medical treatment

Antibiotics

Antibiotics such as ciprofloxacin and metronidazole are broadly used as first-line treatment of perianal fistulas; however, only one randomized, double-blind, placebo-controlled pilot study was

published to evaluate the safety and efficacy of ciprofloxacin and metronidazole as a treatment for active perianal fistulising CD. No significant differences were found after ten weeks of treatment [34]. In addition, re-exacerbations were common after discontinuation of these treatments [34,35]. Monotherapy with antibiotics is therefore not considered to induce complete healing of perianal fistulas.

Immunosuppressants

An open-label study from 2003 showed that perianal fistulas treated with the immunosuppressant azathioprine in combination with eight weeks of antibiotics responded significantly more often than fistulas treated with antibiotics alone [36]. In addition, immunosuppression with azathioprine and 6-mercaptopurine solely has been shown to be effective in the treatment of perianal fistulas (54% response in comparison to 21% in placebo group) [37]. In patients with previous failure or intolerance to 6-mercaptopurine methotrexate seemed an effective option with a 44–56% response rate [38,39]. However, the recurrence rate was high when the dose of methotrexate was tapered or changed to oral administration.

Anti-TNFα agents

Several trials clearly demonstrated the benefit of the anti-tumour necrosis factor alpha (anti-TNFα) agents infliximab, adalimumab and certolizumab pegol for the induction and maintenance of remission in perianal fistulising disease [40–43]. However, a meta-analysis reported no statistically significant difference in the relative risk of fistulas remaining unhealed with anti-TNFα agents versus placebo [44]. On exclusion of short-term follow-up results, the effect of anti-TNFα on fistula healing became significant. Unfortunately, in a retrospective analysis the five-year probability of recurrence of a perianal fistula that was initially healed with infliximab therapy, was estimated at 40.1% [45]. When infliximab was combined with ciprofloxacin a trend to higher response compared to infliximab alone was observed [46]. In the ADAFI trial [47] patients with perianal fistulising CD were treated with adalimumab monotherapy or adalimumab plus ciprofloxacin. After 12 weeks, the treatment with ciprofloxacin was stopped. At that point, a significant higher response and remission rate was reported in the combination group. However, at week 24 no significant difference in fistula healing between the two treatment groups was found. Another possibility is to inject anti-TNFα locally in the fistula tract. In three studies a small number of patients were open-label treated with multiple local injections of infliximab without any reported adverse events of the treatment [48–50]. The remission rate varied among the studies with a sustained remission between 36.4% [49] and 87.5% [50] after approximately one year. However, in the latter study, local injection of infliximab was combined with fistulectomy. Local injections with adalimumab as a treatment for perianal fistulising CD also appeared to be safe [51,52] with remission rates of 75–77.8% [52,53]. No relapse was observed after a mean follow-up time of 17.5 months in one study [52]. Because the results of locally injected anti-TNFα agents are encouraging, it would be worth it to set up randomized controlled studies to evaluate the efficacy of these local treatments for perianal fistulising CD.

5-Aminosalicylic acid, corticosteroids, cyclosporine and tacrolimus

There is no role for 5-aminosalicylic acid and corticosteroids in the treatment of perianal fistulising CD [35]. The same applies to intravenous cyclosporine and oral tacrolimus: clinical response is seen, but transition to oral treatment or stopping the drugs is associated with a high relapse rates [54–56].

Classical surgical treatment

Before elaborating on the optimal surgical treatment technique, it has to be stated that a conservative surgical approach is warranted in most cases: aggressive surgery may result in outcomes that are worse than the CD itself. Faecal incontinence is a feared complication and may occur even after partial sphincter division. Concomitant proctitis has to be taken into account, and therefore, optimal medical therapy to control disease activity is paramount before embarking on surgery.

Fistulotomy and non-cutting setons

The most simple and classical surgical treatment for perianal fistulas is to open the fistula tract widely by fistulotomy and to let the wound heal by granulation (Fig. 4). Fistulotomy in case of simple superficial fistula is successful in up to 80–100% of the cases [11]. Fistulotomy is not preferred in case of a trans- and extra-sphincteric fistula as a part of the sphincters are cut during surgery. For these fistulas a non-cutting seton for initial drainage can best be placed (Fig. 5). This seton will drain the fistula tract and reduce the local inflammation. If the inflammation has diminished, the seton can be removed. However, the majority of the patients need additional surgical therapy, especially when optimal medical treatment does not appear to prevent disease recurrence. Therefore, seton drainage is often a bridge to a more definite surgical treatment.

Mucosal advancement flap (MAF)

When rectal inflammation is limited, the creation of an MAF to cover the internal opening is a good option. This technique can also be applied in case of a rectovaginal fistula with success rates of 54%–71% in two retrospective series [57,58]. The mucosa and submucosa and even sometimes the muscle is mobilized and then advanced over the internal opening. This technically demanding procedure is known be successful in experienced hands in even up to 71% of CD patients [59]. The majority of the MAF-reports are however limited to patients with cryptoglandular disease, obscuring its clinical value in CD patients. Incontinence may occur in 13% and 9% respectively [60].

Fibrin glue

The success rates of sealing the fistula tract with a mix of both fibrin and thrombin are varying. Fibrin can be retrieved from autologous blood but commercial fibrin adhesives are available as well. Optimistic reports on patients with cryptoglandular disease disclose success rates from 68% to 85% at one year [61,62]. Results in CD are less favourable: a randomised trial including 77 patients with moderate disease were randomised between observation after seton removal and fibrin glue administration [63]. After eight weeks, 38% of the glue patients experienced disease remission whereas only 16% did in the observation group.

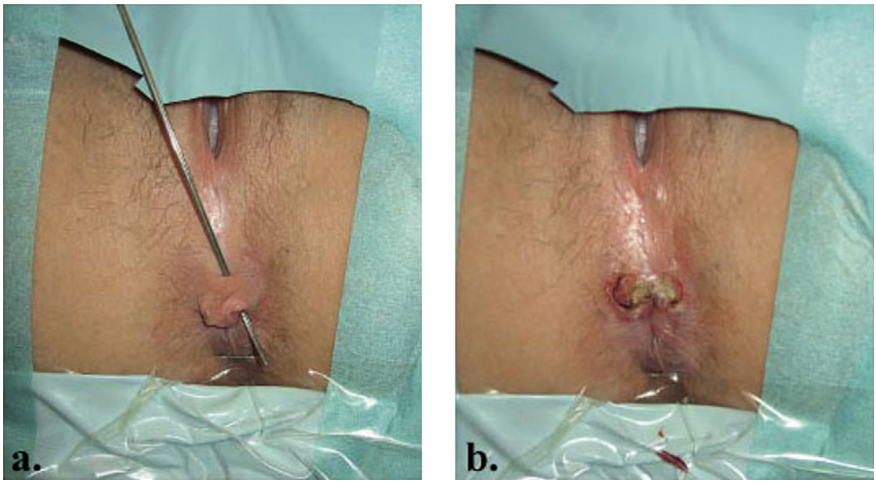

Fig. 4. Fistulotomy of a superficial perianal fistula. (a) The fistula is explored with a probe to find both openings and (b) is opened to heal by granulation. Figure reproduced with permission from Bemelman from van Koperen et al [93].

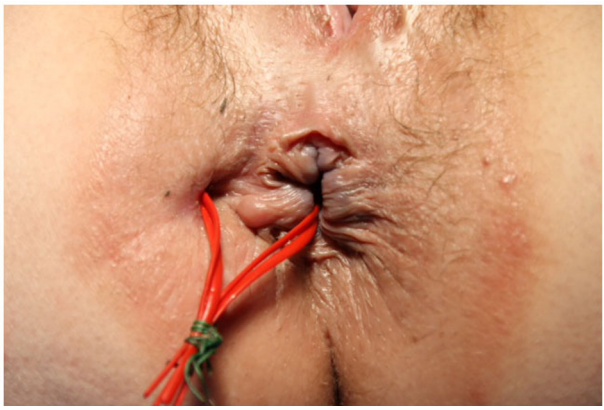

Fig. 5. Non-cutting seton in a perianal fistula to assure drainage and to promote fibrosis of the fistula tract.

Fistula plug

Fistula plugs consist of inert porcine intestinal submucosa that is known to avoid inflammatory reaction after implantation due to its inert nature. After three months the plug is populated with patient's endogenous cells [64,65]. In patients with CD healing rates were 54% [66] without affecting faecal continence [67]. A prospective study was conducted on 73 patients with anorectal fistulas of differing aetiologies. Only eight CD patients were included of which four patients (50%) were successfully managed by plug insertion [61]. Fistula plugs were compared with MAF in two randomised studies, however no CD patients were included. One trial reported poor healing rates in patients with plug insertion (29%) being not statistically different from patients who received an advancement flap (48%) [68]. The other trial was stopped early due dramatic performance of the plug (only 20% success), being much worse than the advancement flap group (88%) [69]. Plug protrusion shortly after surgery is the predominant cause of treatment failure.

Ligation of the intersphincteric fistula tract (LIFT)

This rather new technique was launched by Rojanasakul in 2009 [70] and consists of dissection between the internal and external sphincter up to the level of the fistula tract. There, the fistula is ligated and the rest of the external tract is curetted [71]. The (theoretical) advantage of LIFT over MAF is the complete preservation of sphincter function. LIFT is an emerging technique that has proved to be effective in 57–83% of patients with cryptoglandular disease who had previous unsuccessful treatment [72–74]. There is no randomised comparison with other techniques yet. A small series of 15 CD patients was recently published showing an LIFT healing rate of 67% at 12 months of follow-up without any development of faecal incontinence [75].

Video assisted anal fistula treatment (VAAFT)

VAAFT is a novel technique that has hardly been studied. In only one study VAAFT was applied in CD patients [76]. In 11/13 included patients VAAFT was successfully completed: visualization of the fistula tract and/or side tracts was done using a fistuloscope after which the internal opening was correctly localized under direct vision with irrigation. Additionally, MAFs were created in all patients and in four of 11 patients also faecal diversion was performed. Success rate after nine months was 82% (9/11 patients) with no deterioration in continence. Although promising, this technique still has to prove its value in future studies to come.

Faecal diversion

Only if other options have proved to be ineffective, the construction of a stoma can ameliorate symptoms related to perianal fistulas [77]. Patients should know that many of these stomas, although often considered as a temporary measure, turn out to be definite [78–80].

Proctectomy

If all treatments fail, proctectomy may be considered. These patients suffer from debilitating abscess formation, colonic disease, complex high fistulas and/or anal stenosis. Unfortunately, also proctectomy has the risk of bad wound healing and perianal sinus development in almost 50% of the cases [81].

Potential future therapies

Vedolizumab

Recently Sandborn et al [82] reported the results of the first induction and maintenance trials of vedolizumab, an $\alpha 4\beta 7$-integrin antibody. Although the number of patients with fistulas at baseline in this trial was quite low (165/1115; 14.8%) and the number of patients available for evaluation at week 52 even lower ($\underline{n} = 57$), vedolizumab every eight weeks resulted in a significant higher closure rate (41.2%) compared to placebo (11.1%) ($p = 0.03$) [82].

Mesenchymal stromal cells

A new experimental approach to the treatment of perianal fistula in CD is cellular therapy with mesenchymal stromal cells (MSCs). MSCs are non-haematopoietic precursors of connective tissue cells with immunomodulatory and tissue regenerative properties, making them a potential therapeutic option for inflammatory disorders, including fistulising CD. Several studies indicate soluble factors released by MSCs, such as COX-2-dependent prostaglandin E2 and nitric oxide, to be the main mechanism of MSC-mediated immune suppression. Others believe that cell–cell contact is needed to achieve inhibition of for instance T cell proliferation [83–85]. In the past years several reports on clinical trials using MSCs derived from bone marrow or adipose tissue as a treatment for perianal fistulising CD have been published [86–89]. A phase I trial in which nine fistulas were injected with autologous MSCs derived from adipose tissue, demonstrated 75% healed fistulas after eight weeks without the occurrence of serious adverse events [86]. This trial was followed by a phase II study of the same group [87] in which they included 49 adult patients with complex cryptoglandular ($\underline{n} = 35$) and CD ($\underline{n} = 14$) perianal fistulas. Treatment consisted of either local application of fibrin glue or fibrin glue plus 20 million autologous MSCs derived from adipose tissue. Evaluation took place eight weeks after the treatment and in case of no healing, a second dose of fibrin glue or fibrin glue plus 40 million MSCs was injected. Although the majority of the patients had perianal fistulas based on cryptoglandular disease, overall healing of the fistulas was observed in 16% of the patients who received only fibrin glue versus 71% of the patients who received fibrin glue with additional MSC treatment. An Italian group treated ten patients with refractory fistulising CD every four weeks with a local injection of 20 million autologous MSCs derived from bone marrow as long as the autologous MSCs were available [88]. In 70% of the patients, fistulas closed completely without any serious adverse events. Furthermore, rectal mucosal healing was observed and PDAI was improved. The first paper on the treatment of perianal fistulising CD with allogeneic MSCs was published last year [89]. Patients were treated locally with 20 million MSCs derived from adipose tissue per fistula. If the fistula was not healed after 12 weeks, another 40 million cells were injected. Although the investigators and patients were not blinded, 69.2% of the patients showed a reduction in the number of draining fistulas after 24 weeks. In more than half of the patients complete closure of the treated fistula was achieved and in 30% of the patients complete healing of all fistulas was observed after 24 weeks. However, all these studies were not powered for efficacy analysis, so double-blind randomized controlled trials with a sufficient number of patients are needed in order to prove the actual efficacy of MSCs in the treatment of fistulising CD.

Research targets to improve outcome

Targeting immune cells and genetics

Further unravelling and understanding of predisposing genes and the presence of immune cells and their function in CD fistulas are needed to elucidate the next steps in improving outcome of fistulising CD.

Targeting microbiota

Antibiotics seem partially effective in the treatment of perianal fistulising CD suggesting that microbiota contribute to the development of perianal fistulas. Supporting this hypothesis, faecal diversion leads to long-term improvement of this disease [15]. However, until now only one paper is published on microorganisms found in perianal fistulising CD [16]. It could well be that the bacteria that colonize perianal fistulas in CD are not sensitive to metronidazole or ciprofloxacin. In addition, patients carrying a variant of the nucleotide-binding oligomerizetion domain 2 (NOD2)/caspase recruitment domain 15 (CARD15) tend to respond less to metronidazole or ciprofloxacin than patients with NOD2/CARD15 wild-type [90]. The feasibility of individualized antibiotic therapy should be investigated to improve the outcome of perianal fistulising CD.

Targeting myofibroblasts

Gut myofibroblasts are important players in intestinal tissue damage via the release of matrix metalloproteinases (MMPs) and intestinal wound healing via tissue inhibitors of metalloproteinases (TIMPs). Important for wound healing is the ability of myofibroblasts to migrate. In CD fistulas their migration ability is impaired because of an increased release of TNFα by myofibroblasts. In addition, MMP activity is increased in CD patients resulting in tissue damage and thereby formation of fistulas. Anti-TNF agents enhance migration of myofibroblasts and the increase the production of TIMP-1 resulting in the healing of fistulas by reducing MMP activity [15,91,92]. However, recurrence rates after anti-TNF treatment with consecutive healing are high [45]. Local injections of TIMP-1 could possibly improve outcome and therefore be a target for future investigation.

Targeting epithelial mesenchymal transition (EMT)

On the other hand, the diminished migration capacity of myofibroblasts in CD fistulas may induce EMT to repair mucosal defects by forming a new epithelial layer at the site of tissue damage. However, epithelial cells that undergo EMT become mobile because they lack tight intercellular adhesions, and could therefore be crucial in the pathogenesis of CD fistula development. Evidence for EMT was observed near the luminal origin of enteroenteric, enterovesical, enterocutaneous and perianal fistulas [92], suggesting that EMT-interference could be a novel treatment approach for all types of CD fistulas.

Summary

Although the medical treatment and surgical approaches are improving, the high recurrence rate of perianal fistulas indicates that there is an ongoing need for effective therapies for CD patients with perianal fistulas. Perianal fistulas in CD require specialised and dedicated gastroenterologists and surgeons to optimise treatment outcome. Surgery is often mandatory, but mostly not successful enough and may even deteriorate functional outcome. The increasing number of surgical techniques calls for well-designed clinical trials to establish their true clinical relevance in the treatment of perianal fistulising CD. Apart from surgical expertise a specialized IBD gastroenterology department is necessary to improve patient outcome. In addition, new medical treatment options such as vedolizumab and mesenchymal stromal cells are tested for safety and efficacy in the treatment of perianal fistulising CD. Future targets to improve outcome include genetics, present immune cells, microbiota, myofibroblasts and EMT. For now, a multimodal approach with drugs to keep luminal disease in

remission and to eliminate septic foci together with surgical treatment to reduce symptoms with preservation of faecal continence is advised.

Practice points

- Knowledge about the type, location and route of the fistula and the presence of related abscesses is crucial in the management of perianal fistulising CD and should be obtained with MRI, EUS and/or EUA;
- Spontaneous closure of complex fistula in CD is rare;
- A multimodal approach with both drugs and surgery is recommended in the treatment of complex perianal fistulising CD;
- Achieving complete closure of the fistula tract is a long process with in many cases multiple relapses.

Research agenda

- The safety and efficacy of new therapeutic options for perianal fistulising CD need to be established;
- Future targets to improve outcome include genetics, microbiota, myofibroblasts and EMT;
- New surgical techniques (LIFT, VAAFT) to eradicate perianal fistulas need to be verified in patients with CD.

Conflict of interest

Authors confirm that there are no conflicts of interest.

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