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Managing complex perianal disease after anti-TNF failure: Where to go next?

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ABSTRACT

Crohn's disease is a chronic inflammatory bowel disease that affects various intestinal segments and can involve the perianal region. Although anti-tumor necrosis factor (TNF) agents have revolutionized the management of Crohn's disease and improved the prognosis for patients with perianal Crohn's disease (pCD), their long-term effectiveness is limited: over 60% of patients relapse after one year of maintenance therapy. In recent years, significant advances have been made in the treatment of complex perianal fistulas after anti-TNF failure. Concomitant treatment with antibiotics and immunosuppressants improves the effectiveness of anti-TNF agents. Therapeutic drug monitoring and dose adjustment of anti-TNF therapy (targeting a higher trough level) might also improve treatment response. Novel therapeutic strategies might provide new opportunities for pCD management; for example, ustekinumab might be effective after anti-TNF treatment failure, although more studies are needed. As suggested in recent international guidelines, mesenchymal stem cell injection might be an effective, safe treatment for complex pCD.

1. Introduction

Crohn's disease (CD) is a chronic, inflammatory bowel disease (IBD) that affects various intestinal segments and can involve the perianal region. Perianal Crohn's disease (pCD) can be revealed by various lesions, such as skin tags, fissures, ulcers (primary lesions), fistulas, abscesses (secondary lesions), and strictures. Fistulas are a common manifestation of pCD; 1, 5 and 10 years after the diagnosis of CD, the cumulative incidence is 12%, 15%, and 21%, respectively (Schwartz et al., 2002). Although the pathogenesis of these fistulas is poorly understood, it has been suggested that transmural inflammation and (possibly) luminal bacteria have an important role in fistula onset and perpetuation (Panés and Rimola, 2017). pCD is associated with poor quality of life and a high level of disability. Poor work productivity, sleep disturbance, and sexual dysfunction are frequently reported by these patients, leading to substantial morbidity (Vollebregt et al., 2018; Vester-Andersen et al., 2015; Boudiaf et al., 2021). Furthermore, pCD is associated with more aggressive CD phenotypes and a greater likelihood of anal canal carcinoma, intestinal resection, and definitive stoma (see Fig. 1).

Several systems for classifying perianal fistula have been developed. A simple fistula is defined as a lower tract lesion (superficial, low intersphincteric, or low trans-sphincteric) with a single external opening but no rectovaginal fistulas, anorectal strictures or abscesses. All other fistulas are classified as complex (Sandborn et al., 2003).

Since the primary objective of treating fistulizing pCD is to control infections and induce healing, a multidisciplinary approach (combining surgical drainage and/or non-cutting seton placement) is mandatory prior to the initiation of drug therapy. The long-term goals are to obtain clinical remission and radiological healing, preserve fecal continence, and avoid proctectomy. Although anti-tumor necrosis factor (TNF) agents have revolutionized the prognosis for patients with pCD, their effectiveness is limited: over 60% of patients relapse after one year of maintenance therapy (Sands et al., 2004; Colombel et al., 2007). Lastly, there is still a gap in pCD therapy because sustained remission can only be achieved in half of the patients, despite optimal surgical and drug-based management (Gecse et al., 2014).

As the therapeutic armamentarium is rapidly growing, novel therapeutic strategies might provide new opportunities for the management of pCD. Here, we review the various currently available therapeutic options after anti-TNF treatment failure.

2. Confirm the failure of anti-TNF treatment

Before any change in therapy, anti-TNF treatment failure must be carefully proven through clinical examination, drug monitoring, endoscopic assessment, and (if possible) MRI.

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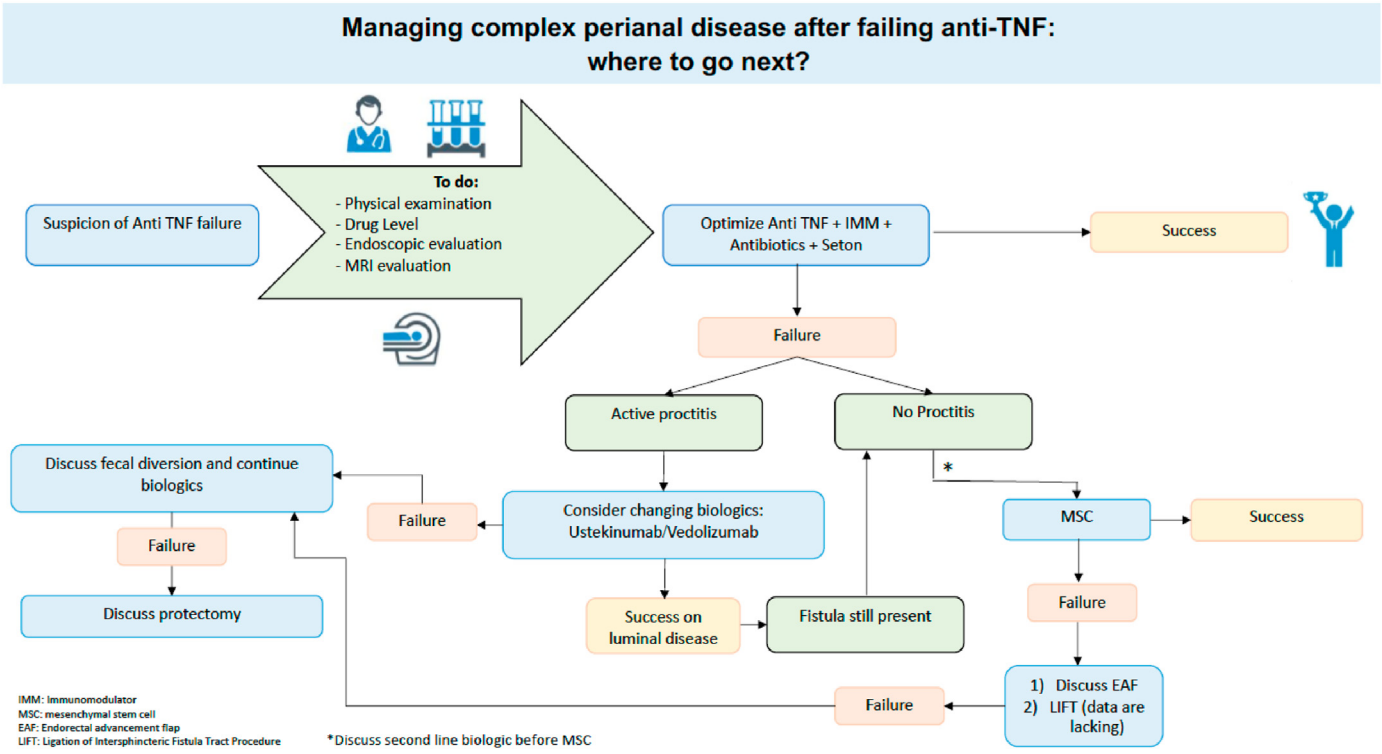

Fig. 1. The use of mesenchymal stem cells currently appears to be the most promising therapy for healing perianal fistulas and changing the outcome of this complex disease.

2.1. The initial work-up

Local infection control is an essential component of medical therapy for pCD. There are different ways of checking for the presence of a deep infection, including examination under anesthesia and MRI. The latter is highly accurate for detecting fistulas and abscesses. It is recommended to drain all perianal abscesses other than sub-centimeter lesions. Drainage has several justifications. Firstly, it prevents sepsis in immunocompromised patients. Secondly, the resolution of abscess-related inflammation is required for fistula healing (Lopez et al., 2019). Adequate drainage is usually achieved by incision combined (when possible) with the placement of a loose seton; this ensures adequate drainage of the fistula's tract and avoid recurrent infections. MRI and examination under anesthesia should be repeated whenever necessary. An endoscopic evaluation of the rectum is also an essential component of the work-up. Proctitis is associated with a lower fistula healing rate and a higher fistula recurrence rate (Bell et al., 2003).

2.2. Optimize anti-TNF therapy

2.2.1. Antibiotics

The efficacy of combining antibiotics with anti-TNFs in pCD has been evaluated in three clinical trials. While all three showed a trend towards a higher response rate before week 24, none of the outcomes were statistically significant at the end of the study period. In a multicenter, double-blind, placebo-controlled trial, the ciprofloxacin-adalimumab combination was evaluated in 76 patients with pCD. By week 12, the clinical response rate was 71% for patients treated with adalimumab plus ciprofloxacin and 47% in patients treated with adalimumab plus placebo ($p = 0.047$). The remission rate was also significantly higher ($p = 0.009$) in the active combination group (65%, vs 33% in the placebo group). At week 24, the intergroup difference in the clinical response was not significant (Dewint et al., 2014). The value of a ciprofloxacin-infliximab combination was evaluated in a small, randomized, controlled trial with 24 patients. At week 18, the response rate was 73% in the ciprofloxacin group and 39% in the placebo group ($p = 0.12$) (West et al., 2004). All these studies might have been underpowered. A recent meta-analysis found low-quality evidence for the efficacy of an anti-TNF-antibiotic combination vs. an anti-TNF alone (Lee et al., 2018). The American Gastroenterological Association recommends the adjunction of an antibiotic to a biologic for the induction of fistula remission (strong recommendation, moderate certainty evidence) (Singh et al., 2021a).

2.2.2. Combination therapy and therapeutic drug monitoring

The results of the SONIC trial demonstrated that an immunosuppressant-anti-TNF combination is more effective than anti-TNF in the treatment of luminal CD (Colombel et al., 2010). Unfortunately, no randomized trials have been reported for pCD. An analysis of two randomized studies of induction or maintenance therapy with infliximab with or without an immunomodulator vs. placebo for pCD did not find a difference in fistula outcomes (Sands et al., 2004; Present et al., 1999). Observational studies of combination therapy vs. infliximab monotherapy have given conflicting results. In a retrospective study, combination therapy was significantly associated with fistula closure (hazard ratio (HR) [95% confidence interval (CI)]: 2.58 [1.16–5.6]; $p = 0.02$) (Bouguen et al., 2013). Combination therapy was associated with a higher anti-TNF trough level and a lower likelihood of anti-drug antibodies. Several retrospective, observational studies have identified the same association in pCD; patients with higher infliximab drug levels had greater fistula response and remission rates. Although the infliximab cut-off differed from one study to another, it appears that the target level should be higher for pCD than for luminal CD. A recent subgroup analysis of the ACCENT II trial showed that a higher infliximab concentration at week 14 was associated with a fistula response (odds ratio (OR) [95%CI]: 1.16 [1.02–1.32]; $p = 0.019$) and a composite remission outcome (defined as complete fistula response plus the normalization of C-reactive protein (CRP) levels; OR: 2.32 [1.55–3.49]; $p < 0.001$) at week 14 (Papamichael et al., 2021). Higher infliximab concentrations at week 14 were also associated with the composite remission outcome at week 54 (OR: 2.05 [1.10–3.82]; $p = 0.023$). An infliximab level $\geq$20 μg/mL at week 2, $\geq$15 μg/mL at week 6, and $\geq$7

μg/mL at week 14 was associated with composite remission at week 14. Similarly, a retrospective study found higher anti-TNF levels in patients with radiological remission than in patients with active disease (respectively 7.4 vs. 3.9 μg/mL for infliximab, $p < 0.05$; 9.8 vs. 6.2 μg/mL for adalimumab, $p = 0.07$) (De Gregorio et al., 2021). Anti-infliximab antibodies were much more common in patients with active fistulas than in patients with healed fistulas (29.6% vs. 1.6%, respectively). The study by Yarur et al. showed that the odds of achieving fistula healing were 8 times greater in patients who underwent infliximab dose escalation (Yarur et al., 2017).

Taken as a whole, these data suggest that "proactive drug monitoring" and then dose adjustments in patients with low levels is associated with higher fistula healing rates. However, data from randomized controlled trials are lacking. Given the impact of immunosuppressants on anti-TNF immunogenicity and the fact that higher anti-TNF agent levels have been linked to a higher response rate in pCD, combination therapy should be considered in all pCD patients treated with an anti-TNF drug.

3. Drug therapy after anti-TNF treatment failure

3.1. Vedolizumab

The α4β7 integrin antibody vedolizumab inhibits the trafficking of subpopulations of T cells to the gut mucosa. The presence of $\alpha4\beta7^+$ T cells in perianal fistula tracts was recently reported. The curettage material from seven CD patients with perianal fistula tracts contained a significant number of T cells, of which 69% were $CD3^+$ $\alpha4\beta7^+$ (de Krijger et al., 2018). These findings support the clinical testing of vedolizumab in pCD, since no data from randomized, placebo-controlled trials are available. The initial data on vedolizumab's efficacy in pCD came from exploratory analyses of data from the GEMINI 2 study of 461 responders to a 6-week course of vedolizumab induction therapy who then received maintenance therapy with vedolizumab or a placebo (Feagan et al., 2018). Twenty-eight percent of the vedolizumab-treated patients had fistula closure at week 14, compared with 11% of the patients treated with placebo. At week 52, the rate of fistula closure was higher in the vedolizumab group (33%, vs 11% in the placebo group; HR [95%CI]: 2.54 [0.54–11.96]). In 2020, the initial results of the ENTERPRISE study were presented. This is a double-blind, randomized phase IV trial of two vedolizumab dosing regimens (doses at 0, 2, 6, 14, and 22 weeks, or the same regimen plus an additional dose at week 10) in pCD (Schwartz et al., 2020). The primary endpoint was the proportion of patients with at least a 50% reduction from baseline in the number of draining fistulas at week 30. Twenty-eight of the 32 patients had one or more draining fistulas at baseline. At week 30, 54% of patients had achieved the primary endpoint (64.3% for the regimen without the week 10 dose, and 42.9% for the regimen with the week 10 dose). Closure of all draining fistulas at baseline was observed in 43% of the patients at week 30 (50% for the regimen without the week 10 dose; 36% for the regimen with the week 10 dose).

A recent multicenter study of the *Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif* (GETAID) assessed the effectiveness of vedolizumab in a real-life cohort of 102 patients with pCD. Efficacy was defined as clinical success (no draining fistula at clinical examination, and no anal ulcers for primary lesions) at 6 months in the absence of drug therapy or surgical treatment for pCD (Chapuis-Biron et al., 2020a). Success was achieved in 22.5% of the patients. Among patients with setons at baseline, removal was possibly in 15%. In a multivariable analysis, the factors associated with treatment success were three or more previous biologics (OR [95%CI]: 0.20 [0.04–0.98]) and no antibiotics at initiation (OR: 4.76 [1.25–18.19]). Recurrence was observed in 15 (30%) of the 49 patients with inactive pCD, after a median of 22 weeks. A radiologic response was achieved in 38% of the patients having undergone pelvic MRI during follow-up (Table 1).

On the basis of these data, there appears to be too little evidence in favor of the widespread use of vedolizumab after anti-TNF treatment failure in pCD. Further dedicated studies are needed. The use of vedolizumab is not included in formal guidelines on the treatment of pCD (Torres et al., 2020).

3.2. Ustekinumab

Ustekinumab (a fully humanized IgG monoclonal antibody that blocks the p40 subunit common to interleukins 12 and 23) has been approved for the treatment of moderate-to-severe active CD. However, data on ustekinumab's efficacy in pCD are scarce. The ongoing GETAID-sponsored Ustekinumab in Fistulizing Perianal Crohn's Disease (USTAP) trial (NCT04496063) is the only randomized controlled trial of ustekinumab in pCD. A post-hoc analysis of pooled data from the CERTIFI, UNITI-1 and UNITI-2 trials suggested that ustekinumab was efficacious in pCD, with higher fistula closure rates in patients treated with ustekinumab (24.7%, vs 14.1% in nontreated patients) after 8 weeks (Battat et al., 2017). Ustekinumab's efficacy has been described in several studies of small numbers of patients with pCD (Table 2). In a Dutch observational prospective cohort study, 28 patients (12.7%) with one or more active peri-anal fistulas at baseline were included (Biemans et al., 2020). After 12 weeks of treatment, four patients (14.3%) showed complete clinical remission, and four (14.3%) patients showed a treatment response (based on a decrease in fistula drainage); after 24 weeks of treatment, these percentages were respectively 35.7% and 14.3%. A Spanish retrospective cohort study reported that ustekinumab was efficacious in 116 patients with CD, of whom 18 have active perianal fistulas. pCD improved in up to 76% patients after 6 months of treatment (Khorrami et al., 2016). In a Canadian multicenter cohort, 22 out of 45 patients (49%) with active perianal lesions at the time of ustekinumab induction achieved a clinical response at the end of the 45-week follow-up period, and 12 out of 45 (27%) were in remission (Ma et al., 2017). In a Scottish retrospective study that included 37 patients with active perianal disease, the 12-month response rate was 53% (Plevris et al., 2021).

The GETAID conducted a national multicenter retrospective cohort study in 207 patients with either active or inactive pCD at ustekinumab initiation (Chapuis-Biron et al., 2020b). 99% of the patients had already been exposed to at least one anti-TNF agent, and 58 (28%) had already been exposed to vedolizumab. In patients with active pCD at ustekinumab initiation and no additional drug-based or surgical treatments for pCD, success at 6 months was defined as the physician's clinical judgment. Fifty-six (27%) patients discontinued ustekinumab after a median of 43 weeks. Success was achieved in 39% of the patients with active pCD. Among the patients with setons at initiation, removal was possible in 33% of cases. A recent retrospective study evaluated the effectiveness of ustekinumab optimization every 4 weeks in patients with a partial response or a secondary loss of response to ustekinumab (Fumery et al., 2021). A short-term clinical response and short-term clinical remission were observed in 61% and 31% of the patients, respectively. Sixteen (16%) of the 100 patients underwent ustekinumab intensification for perianal disease and 7 (7%) underwent intensification for both perianal and luminal CD; 14 (61%) of these 23 patients displayed an immediate response, according to the investigating physician. At last follow-up, perianal fistula closure was observed in 22% of the patients. In contrast, four patients experienced worsening of pCD and required perianal surgery during follow-up. In the GETAID study, concomitant immunosuppressive treatment was not associated with efficacy of ustekinumab (Chapuis-Biron et al., 2020b). In contrast to anti-TNF agents, the ustekinumab concentration did not appear to be influenced by the concomitant administration of immunosuppressants. In a recent meta-analysis, we found that combining vedolizumab or ustekinumab with an immunomodulator was no more effective than monotherapy for the induction or maintenance of remission (Yzet et al., 2021a).

Lastly, Attauabi et al. performed a meta-analysis of nine studies with a total of 396 ustekinumab-treated pCD patients (Attauabi et al., 2021a). The pooled proportions of patients with a fistula response were 41%, 40% and 55% at weeks 8, 24, and 52, respectively. For fistula remission, the pooled proportions were respectively 17%, 18%, and 16.7% at these

Table 1
Summary of studies of vedolizumab's efficacy in perianal fistulizing disease.

	Study design	Number of patients	Endpoints	Response rate	Follow-up period or timepoints
Dulai, 2016 (Dulai et al., 2016)	Retrospective	212	Clinical remission	Baseline perineal disease was associated with a lower clinical remission rate (HR [95% CI] = 0.49 [0.27–0.88])	Median follow-up: 39 weeks
Feagan, 2018 (Feagan et al., 2018)	Prospective, post-hoc	210	Fistula closure	Fistula closure rate of 28% and 33% at weeks 14 and 52, respectively, compared with 11% and 11% in the placebo group.	Weeks 14 and 52
Schwartz, 2020 (Schwartz et al., 2020)	Prospective	32	Clinical response: ≥50% reduction from baseline in the number of draining fistulas	Clinical response rate = 46.4% Fistula closure rate = 42.9%	Week 30
Chapuis-Biron, 2020 (Chapuis-Biron et al., 2020a)	Prospective	102	Clinical success MRI response	Clinical success rate = 22.5% Radiologic response rate = 38.4%	Week 26

Table 2
Summary of studies of ustekinumab's efficacy in perianal fistulizing disease.

	Study design	Number of patients	Endpoints	Response rate	Follow-up period or timepoints
Battat, 2017 (Battat et al., 2017)	Prospective, post Hoc	6	Clinical response = >50% reduction from baseline in the number of draining fistulas. Clinical remission = closure of all fistulas	Clinical response rate = 66% Clinical success rate = 33%	6 months
Khorrami, 2016 (Khorrami et al., 2016)	Retrospective	18	Clinical response	Clinical response rate = 61%	6 and 12 months
Plevris, 2021 (Plevris et al., 2021)	Retrospective	37	A reduction in enhancement, closure, or fibrosis of the tract, compared with baseline MRI	A response rate of 12.5% at 6 months and 53.1% at 12 months	6 and 12 months
Straatmijer, 2021 (Straatmijer et al., 2021)	Prospective	29	Fistula remission	Fistula remission rate = 17.2%, 37.9% and 37.9% after 12, 24 and 52 weeks	Weeks 12, 24 and 52
Attauabi, 2021 (Attauabi et al., 2021b)	Prospective	18	Clinical response and remission	The clinical response rate was 53.8%, 50.0% and 63.6% at weeks 16, 24 and 52, respectively. No fistula remissions.	Weeks 8, 24 and 52
Chapuis-Biron, 2020 (Chapuis-Biron et al., 2020b)	Retrospective	148	Clinical success MRI response	Clinical success rate = 38.5% MRI response rate = 50%	6 months
Biemans (2020) (Biemans et al., 2020)	Prospective	28	Fistula remission = resolution of all peri-anal fistulas in a physical examination. Fistula response = reduction 50% in the number of actively draining fistulas	Clinical remission rate = 14.3% and 35.7% at weeks 12 and 24, respectively Clinical response rate = 14.3% and 14.3% at weeks 12 and 24, respectively	12 and 24 weeks
Ma (2017) (Ma et al., 2017)	Retrospective	45	Fistula response = reduction 50% in the number of actively draining fistulas Fistula remission = complete absence of fistula drainage and closure of all fistulas in a physical examination.	Clinical response rate = 48.9% Clinical remission rate = 26.7% Transmural healing rate = 31.1%	Median follow-up of 45.6 weeks
Fumery (2020) (Fumery et al., 2021)	Retrospective	23	Fistula response: clinical judgment Fistula remission: closure of fistula	Clinical response rate = 61% Clinical remission rate = 22%	Median follow-up of 8.2 months

timepoints. In conclusion, the data from several observational studies suggest that ustekinumab is beneficial in patients who have failed to respond to anti-TNF agents. However, given that the level of evidence is relatively low, the results of the USTAP study are eagerly awaited.

3.3. Mesenchymal stem cell therapy

The management of fistulizing pCD has been revolutionized by the recent advent of mesenchymal stem cell (MSC) therapy. This approach is based on the assumption that fistulas result from epithelial defects and are maintained by continued inflammation in the fistula tract. The ADMIRE trial has paved the way by evaluating the effectiveness and safety of darvadstrocel in CD patients with refractory, complex, draining perianal fistulas (Panés et al., 2016). To ensure homogeneity, the study procedures were standardized. Firstly, patients underwent an examination under anesthesia, fistula curettage, and seton placement at least 2 weeks before darvadstrocel or placebo administration. At the treatment administration visit, setons (if present) were removed and all internal openings were closed. Next, patients received an injection of darvadstrocel or placebo in the tissue adjacent to the fistula tracts and internal openings. The primary endpoint at week 24 was defined (after a clinical assessment) as the closure of all treated external openings that were draining at baseline, and the absence of collections >2 cm from the treated perianal fistulas (as confirmed by MRI). Two-hundred and twelve patients were included. The primary endpoint was reached in 50% and 34% of the patients treated with darvadstrocel or placebo, respectively. To determine the long-term efficacy of MSC therapy, 131 participants were followed up for 52 weeks (Panés et al., 2018). A slight increase in the proportion of patients with improvement was observed in the darvadstrocel treatment group. High remission rates were observed in the placebo group, which emphasizes the importance of adjunctive surgical techniques in pCD. Seventeen percent of the patients in the darvadstrocel group and 29% of the patients the placebo group experienced treatment-related adverse events, the most common of which were anal abscesses. In summary, darvadstrocel is the first treatment since infliximab to have demonstrated efficacy in a randomized controlled trial in patients with pCD. In 2018, darvadstrocel was approved in Europe in patients who have failed to respond to conventional or biologic drugs.

Whereas darvadstrocel's MSCs are derived from allogeneic adipose tissue, some other preparations have been developed. Allogeneic bone-marrow-derived MSCs have also showed promising results, with a reduction in the number of draining fistulas in a small (n = 31 patients) randomized controlled trial (Molendijk et al., 2015). A study in 12 patients reported similar results, with sustained, complete closure in 7 patients and incomplete closure in 3 patients (Ciccocioppo et al., 2011). Although injections of cultured autologous and allogeneic adipose-tissue-derived stem cells are effective, this treatment is expensive and its preparation is time-consuming. Some authors have reported the effects of injecting freshly collected autologous adipose tissue into patients with CD. Dig et al. injected freshly collected autologous adipose tissue into 21 patients with CD and complex perianal fistulas (Dige et al., 2019). Six months later, 12 of the patients (57%) showed complete fistula healing. Three patients (14%) reported no fistula secretion, and 1 patient (5%) reported reduced secretion. Of the 10 patients with trans- or inter-sphincter fistulas, MRI showed complete fistula resolution in 9 cases and a markedly reduced gracile fistula in the remaining case.

Laureti et al. treated 15 biologic-refractory patients with CD and complex perianal fistulas with microfragmented autologous adipose tissue using a commercially available system. The system provided microfragmented tissue intra-operatively without the need for expansion and/or enzymatic treatment. It also washed away pro-inflammatory oil and blood residues, while protecting the stromal vascular niche (Laureti et al., 2020). At week 24, 10 patients showed combined clinical and radiological remission, 4 patients showed improvements, and one patient failed to respond to this treatment.

Other researchers have exploited the adipose-derived stromal vascular fraction – an easily accessible source of cells with angiogenic, immunomodulatory and regenerative properties. After initial liposuction, a second operation involved microfat harvesting with a closed-circuit filtration system, preparation of the fistulas (seton removal, curettage of fistula tracts, and suturing of the internal openings), and the immediate injection of both the microfat and the adipose-derived stromal vascular fraction into the wall of the fistula. Seventy percent of the treated patients showed a clinical response at week 12, and 80% showed a response at week 48. Respectively 20% and 60% of the patients achieved combined remission at weeks 12 and 48 (Serrero et al., 2019).

Although favorable safety profiles for MSCs were reported in these studies, long-term safety data are scarce. Barnhoorn et al. reported on an Epstein-Barr-virus-associated B cell lymphoproliferative lesion in the rectum of a patient 4 years after the local administration of bone-marrow-derived MSCs (Barnhoorn et al., 2019). Lastly, no neoplastic complications were observed during the long-term follow-up of the ADMIRE trial.

MSCs were therefore recently included in the international guidelines on pCD. The European Crohn's and Colitis Organisation (ECCO) guidelines suggest that allogeneic adipose-derived stem cell therapy is an effective, safe treatment for complex perianal fistulas in patients with CD and that treatment with autologous adipose-derived stem cells can have benefits for patients with complex perianal fistulas (Adamina et al., 2020). However, more data are needed to confirm the efficacy and safety of freshly collected autologous adipose tissue.

3.4. Hyperbaric oxygen therapy

Hyperbaric oxygen (HBO) therapy has proven its efficacy for the treatment of chronic wounds. During the 1990s (i.e. before the biologic era), HBO was evaluated in studies of small cohorts of patients with pCD. Some impressive results were reported, with clinical improvement rates of up to 80% (Colombel et al., 1995; Lavy et al., 1994). More recently, Feitosa et al. evaluated the efficacy of HBO in 25 patients with pCD; after a median of 43 HBO sessions, the researchers observed complete healing (defined as the closure of external orifices) in 80% of patients (Feitosa et al., 2021). Similar results were reported in 20 patients who received 40 HBO sessions over an 8-week period (Lansdorp et al., 2020). Twelve patients showed a clinical response (60%) and four (20%) showed clinical remission as assessed by fistula drainage. The median CRP and fecal calprotectin levels decreased from 4.2 to 2.2 mg/mL and from 399 to 31 μg/g, respectively. A recent meta-analysis reported complete and partial healing of fistulas in respectively 48% and 34% of the pCD patients (Singh et al., 2021b). With a view to confirming these results, the performance of a randomized controlled trial is now warranted. HBO therapy appears to safe and well tolerated. In a systematic review of studies of HBO in patients with IBD, Dulai et al. reported that the incidence of adverse events per 10000 treatments was 10 overall, 1.1 for bilateral ear drum perforations, 1.1 for middle ear barotrauma, 1.1 for blurred vision, and 6.7 for psychological intolerance (Dulai et al., 2014). No episodes of pneumothorax, seizure, bowel perforation or other serious adverse events were reported (Dulai et al., 2014).

3.5. Combinations of biologics

Several case-series have reported on the effectiveness of this strategy in CD, ulcerative colitis, and other immune-mediated inflammatory diseases. The only randomized controlled trial of combination therapy in IBD assessed infliximab and an anti-integrin agent (natalizumab) and did not find a safety signal relative to infliximab monotherapy (Sands et al., 2007). Although a growing body of evidence suggests that the combination of biologics can be effective, the largest published study included only 22 patients with IBD (Yang et al., 2020). Given the limited number of effective therapeutic options in pCD, the preliminary data on the efficacy of combinations of biologics appears to be promising. However, further studies are urgently needed before biologic agents can be combined on a routine basis.

4. Surgical treatment

Fistula closure strategies have three objectives: reduce the discomfort linked to the persistence of liquid or gas overflows, decrease the risk of recurrent suppuration, and limit the risk of long-term incontinence. It was demonstrated that a multidisciplinary approach was associated with a higher fistula healing rate and a lower relapse rate. Recently, the results of the PISA II trial confirmed that surgical closure following anti-TNF induction treatment induces healing (on MRI) more frequently than anti-TNF alone (Meima - van Praag et al., 2021). Fistula closure can be considered only when fistulas are well drained, not inflammatory or not very inflammatory and in the absence of residual collections and active rectal disease. Various surgical procedures have been suggested with a view to achieving this objective.

4.1. Endorectal advancement flap

Endorectal advancement flap (EAF) is the most common surgical technique in cases of complex perianal fistula. The procedure involves the mobilization of a U-shaped flap of rectal mucosa, submucosa, and muscle fibers for closure of the internal orifice. Jones at al. reported a 58% clinical success rate for EAF in CD patients (Jones et al., 1987). However, patients with active proctitis were excluded from the study, and 9 (47%) of the 19 patients required a temporary diverting stoma. Recently, a retrospective study observed closure of the external opening without discharge in up to 60% (12 out of 20) of patients and radiological healing in 50%, after a median of 6 months (van Praag et al., 2020). Fistulas recurred in 19% of the patients, after a median of 14.5 months. Although the technique was safe, 21% developed post-operative incontinence. A systematic review found that the pooled success rate was 61% and the incontinence rate was 8% (Stellingwerf et al., 2019). Small bowel involvement, severe active proctitis, and stoma diversion prior to EAF were associated with lower success rates (Joo et al., 1998; Makowiec et al., 2005; Roper et al., 2019). The ECCO guidelines suggest that EAF is an option for CD patients with complex fistulas (Adamina et al., 2020).

4.2. Ligation of the intersphincteric fistula tract

Ligation of the intersphincteric fistula tract (LIFT) has been developed as a sphincter-sparing technique for the treatment of non-CD-related perianal fistula. This procedure involves opening of the intersphincteric groove, dissection of the fistulous tract, and ligation of the tract with interrupted sutures. Sirany et al. performed a systematic review of the efficacy of LIFT procedure in all indications (Sirany et al., 2015). The primary healing rates ranged from 47% to 95% (Gingold et al., 2014). A recent meta-analysis compared EAF with LIFT in the treatment of pCD; the difference in the overall success rate was not statistically significant. Incontinence rates were significantly higher after EAF (7.8%) than after LIFT (1.6%) (Stellingwerf et al., 2019). Recently, the Amsterdam group conducted a retrospective cohort study of the effectiveness and safety of 19 LIFT procedures and 21 EAF procedures; the clinical healing rate was higher (albeit not significantly) in the LIFT (89%, vs 60% for EAF; p=0.065]. The recurrence rate (21% and 19% for LIFT and EAF, respectively) and radiological healing rate (52% vs 47%, respectively) were similar in the two groups (van Praag et al., 2020). Postoperative incontinence was reported after respectively 16% of LIFT procedures and 21% of EAF procedures, The ECCO has suggested that given the paucity of data, the LIFT procedure does not have clear value in the treatment of pCD (Adamina et al., 2020).

4.3. Fibrin glue

Fibrin glue has not been extensively studied in an indication of CD. In 2010, Grimaud et al. reported the results of a multicenter, randomized, open-label trial including 77 patients with pCD randomized to either fibrin glue or observation (Grimaud et al., 2010). At 8 weeks, healing was more likely in the fibrin glue group (38%, vs. 16% in the observation group; p = 0.04). The benefit was especially observed in patients with simple fistulas. In another small study of the efficacy of fibrin glue in refractory pCD, 10 (71%) of the 14 patients no longer required drainage and 1 patient (7%) required less drainage 3 months after fibrin glue injection. After 2 years, 8 (57%) of the 14 patients had complete fistula closure and no long-term adverse events (Vitton et al., 2005). In view of these limited data, the ECCO guidelines state that fibrin glue may be a potential treatment with limited efficacy for patients with complex pCD (Adamina et al., 2020).

4.4. Fistula plug placement

Anal fistula plugs are designed to close the internal orifice of the tract and to create a scaffolding for the ingrowth of healthy tissue. Data for patients with CD are scarce. In a French open-label trial, 54 patients were randomized to seton removal only vs. fistula plug placement. At week 12, the incidence of fistula closure was similar in the two groups (32% in the plug group vs. 23% in patients with seton removal only; p = 0.19) (Senéjoux et al., 2016). Interestingly, a phase I study of 12 patients evaluated the effectiveness of applying autologous adipose-derived stem cells to a fistula plug. At 6 months, clinical and MRI healing was observed in 10 of 12 patients [83%] (Dietz et al., 2017). The ECCO guidelines consider that anal fistula plugs should not be considered routinely in pCD because seton removal alone is equally effective (Adamina et al., 2020).

4.5. Fecal diversion

Fecal diversion has long been considered the definitive therapy for refractory pCD. In a historical cohort, up to 31% of patients with perianal disease required a permanent stoma (Mueller et al., 2007). In the biologic era, fecal diversion can also be considered as a temporary measure for increasing the drugs' efficacy (Bafford et al., 2017). In one study, fecal diversion was evaluated in 30 patients with diversion for perianal disease (37%), colonic disease (33%), or both (30%). Overall, fistula closure was observed in 70% of those who underwent diversion for colonic disease and only 25% of those with perianal disease. Twenty percent of the patients ultimately required colectomy. A recent study evaluated the long-term outcomes of 82 patients with fecal diversion with or without proctectomy (McCurdy et al., 2021). Fistula healing occurred more frequently after diversion with proctectomy (in 83% of cases) than after diversion without proctectomy (53%). Biologics were independently associated with stoma closure and the avoidance of proctectomy. In a meta-analysis, Singh et al. investigated the frequency of a response to fecal diversion and bowel continuity after fecal diversion for pCD (Singh et al., 2015). Restoration of bowel continuity was attempted in only one third of patients after fecal diversion, with clinical success observed in only 17% of cases. Overall, 41% of patients required proctectomy after the failure of temporary fecal diversion. The absence of rectal involvement was the main factor associated with stoma closure. At present, there are no published data on the effectiveness of the combination of fecal diversion and MSC therapy in patients with refractory pCD. All these data suggest that although fecal diversion surgery remains an option after the failure of treatment with a biologic, the likelihood of restoring bowel continuity remains low.

5. Endoscopic therapy

Endoscopy is the cornerstone IBD management technique, from diagnosis to therapeutic decision-making. The role of endoscopy in stricture management is now well defined, and balloon dilations are routinely performed for CD strictures. Conventionally, CD fistulas and abscesses are treated with drugs and surgery. Thanks to technical progress, endoscopic fistulotomy, incision, drainage and even seton placement can be performed. Endoscopy is considered to be a minimally invasive procedure, whereas surgery treatment has been linked to a risk of stricture, anastomotic leakage, sinus, fistula, or abscess. Several small studies have described the closure of gastrointestinal defects with an over-the-scope clip system (OTSC), with a long-term success rate of 60% (Haito-Chavez et al., 2014). With regard to CD, few case reports or case series have covered the potential value of OTSC for closing anastomotic leaks after ileal pouch anal anastomosis, enterocutaneous fistulas or (more recently) anal fistulas (Wei et al., 2017; Yzet et al., 2021b). In a small, retrospective study of an OTSC in 10 patients with refractory anal fistula, 6 patients had CD; after a median of 72 days, the reported fistula closure rate was 70% (7 out of 10) (Mennigen et al., 2015). Some researchers have suggested combining dissection of the epithelium around the fistula opening with OTSC-based fistula tract closure, in order to promote fusion of the apposed tissue before clip placement at the edge of the fistula (Matano et al., 2019; Wallenhorst et al., 2019). This idea came from surgical fistula curettage, which has a high fistula closure rate. Endoscopic suturing devices have recently become available but their use in CD patients has not yet been described.

6. Conclusion

In the biologic era, the management of complex fistulas is still challenging. In recent years, significant progress has been made in understanding the optimal treatment approach for pCD. Anti-TNF agents remain the best-established treatment option. Concomitant antibiotic and immunosuppressant therapy improves the effectiveness of anti-TNF agents. Anti-TNF therapeutic drug monitoring and dose adjustment (targeting a higher trough level) might increase the treatment response rate. Novel therapeutic strategies might provide new opportunities for pCD management: for example, ustekinumab might be effective after anti-TNF treatment failure, although more studies are needed. As suggested in recent international guidelines, mesenchymal stem cell injection might be an effective, safe treatment for complex pCD. Bearing in mind the failure rate of all these treatment options, novel therapeutic strategies are eagerly awaited.

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Declaration of competing interest

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