Best Practice & Research Clinical Gastroenterology xxx (2018) 1–9

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

Refractory ulcerative proctitis: How to treat it?

Guillaume Pineton de Chambrun [a, *], Barbara Tassy [a], Laura Kollen [b], Gaspard Dufour [a], Jean-Christophe Valats [a], Michael Bismuth [a], Natalie Funakoshi [c], Fabrizio Panaro [d], Pierre Blanc [a]

[a] Department of Gastroenterology, Saint-Eloi Hospital, Montpellier University Hospital, Montpellier University, Montpellier, France
[b] Department of Pediatrics, Arnaud de Villeneuve Hospital, Montpellier University Hospital, Montpellier University, Montpellier, France
[c] Department of Gastroenterology, Mersey Community Hospital, Tasmanian Health Service North West Region, Latrobe, Tasmania, Australia
[d] Department of Digestive Surgery and Transplantation, Saint-Eloi Hospital, Montpellier University Hospital, Montpellier University, Montpellier, France

ARTICLE INFO

Article history:
Received 5 February 2018
Received in revised form
25 April 2018
Accepted 10 May 2018

Keywords:
Refractory ulcerative proctitis
Inflammatory bowel disease
Anti-TNF
Azathioprine
Surgery
Treatment

ABSTRACT

Ulcerative proctitis is defined as a mucosal inflammation limited to the rectum. Ulcerative proctitis is responsible for distressing symptoms and alteration of patient quality of life. Effective treatment is important to prevent or delay proximal extension of the disease and to improve quality of life. Refractory ulcerative proctitis is defined as the failure of topical and oral 5-aminosalicylic acid and corticosteroids. Medical management of refractory ulcerative proctitis may be challenging as there is little evidence regarding drug efficacy in this clinical situation. Data are currently available for azathioprine, topical tacrolimus and *anti*-TNF monoclonal antibodies as rescue treatment for refractory ulcerative proctitis. Other biologics may be of benefit despite a lack of dedicated clinical trials. Ultimately, experimental therapies such as epidermal growth factor enemas, appendectomy or fecal transplantation may be tried before restorative proctocolectomy with J pouch anastomosis, which has demonstrated good results with regards to clinical remission and quality of life.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by intestinal inflammation limited to the rectal and colonic mucosa [1]. UC typically involves the distal part of the rectum and may extend proximally with continuous lesions. According to the Montreal classification and depending on disease extent, UC is classified as proctitis (E1, inflammation limited to the rectum), left-sided colitis (E2, inflammation terminating at the splenic flexure) or pancolitis (E3, inflammation extending proximally beyond the splenic flexure) [2].

The incidence rate for UC varies from 0.5 to 24.5 per 100,000 person-years worldwide [3,4]. Previous epidemiological studies have shown that 25%–55% of patients with UC present an ulcerative proctitis (UP) at the time of first diagnosis [5–8]. Although it is generally assumed that this condition represents the benign end of the spectrum of UC, it is responsible for many distressing symptoms including increased stool frequency, tenesmus, urgency and bleeding, and clearly alters patient quality of life [7,9]. Moreover, proximal extension of UP may occur in up to 28% of patients after 5 years follow-up with progression to extensive colitis in 4–10% of cases [7,10–12]. In a recent population-based study, it was also demonstrated that 25% of UC pediatric patients had UP at diagnosis and that 49% of them presented colonic extension at maximal follow-up [13].

Effective treatment of UP is important to prevent or delay proximal extension of the disease [14,15]. Indeed, chronic, continuous and relapsing forms of UP have been associated with extension of mucosal inflammation [16]. Thus, the short-term goal of UP treatment is to induce rapid clinical and endoscopic remission and the long-term goal is to maintain this remission and prevent disease extension. Topical 5-aminosalicylic acid (5-ASA) administered as suppositories is the preferred initial treatment for mild or moderately active proctitis [10]. In patients with persistent disease despite topical 5-ASA therapy, the next treatment step will be a combination of topical and oral 5-ASA, with the addition of topical and/or oral corticosteroids if necessary.

Refractory UP could be defined as patients with endoscopically

* Corresponding author. Dept. of Gastroenterology, Saint-Eloi Hospital, Montpellier University Hospital 80 Av. Augustin Fliche, F-34295, Montpellier, France.
E-mail address: g-pinetondechambrun@chu-montpellier.fr (G. Pineton de Chambrun).

https://doi.org/10.1016/j.bpg.2018.05.009
1521-6918/

documented active proctitis, who fail oral corticosteroids combined with oral and rectal 5-ASA therapy [17]. Medical management of this patients may be challenging as there is very little evidence regarding drug efficacy in this clinical situation [18]. Indeed, patients with UC limited to the rectum are systematically excluded from randomized clinical trials, and proof of treatment efficacy in UP is extrapolated from data on extensive colitis or comes from small open label clinical trials [19,20]. Drugs which may be used in the treatment of refractory UP are azathioprine (AZA), cyclosporine (CsA), tacrolimus, and *anti*-TNF monoclonal antibodies [10].

In this review, we will summarize the data regarding the management of refractory UP focusing on available therapies and surgery. We will also explore some experimental therapies which have been proposed for the treatment of refractory UP and we will briefly discuss cancer risk in these patients and its surveillance.

2. Definition of refractory ulcerative proctitis

The gold standard treatment for UP is the use of topical 5-ASA [17]. Indeed, a meta-analysis of 11 trials in 778 patients demonstrated that topical applications (enema or suppositories) of 5-ASA induced clinical remission in active UP and distal colitis in 31–80% (median 67%) of patients compared to 7–11% of patients treated with placebo [21]. More recently, a Cochrane systematic review of 38 clinical trials investigating treatment of distal colitis confirmed the superiority of topical 5-ASA over placebo for the induction of clinical and endoscopic remission with a pooled odds ratio of 8.3 for symptomatic remission (8 trials, 95% CI]4.28–16.12; $p < 0.00001$) and of 5.3 for endoscopic remission [7 trials, 95% CI: 3.15–8.92; $p < 0.00001$) [22]. Suppositories are considered the best formulation for proctitis as they target the site of inflammation better [23]. Indeed, the maximum extent of action of enemas is more from 11 to 40 cm from the anal verge than in the rectum. Regarding administration of suppositories, it was shown that once daily mesalazine topical therapy was as effective as divided doses and was also better tolerated [17,24]. Considering the dose of mesalazine, no dose response has been observed for topical therapy above 1 g of 5-ASA daily [22,25]. A 2013 multicenter, double-blind, randomized placebo-controlled trial investigated the efficacy of 1 g mesalazine suppository or placebo for induction of endoscopic remission in 129 mild-to-moderate UC patients with rectal inflammation. After 4 weeks of treatment, the endoscopic remission rate was significantly higher in patients treated with mesalazine compared to patients treated with placebo (83.8% versus 36.1%; $p < 0.0001$; respectively) [26].

Only one study compared the efficacy of oral versus topical 5-ASA in patients with UP [27]. This was a four-week randomized, controlled, single-center, investigator-blinded study which investigated the efficacy of oral mesalazine (800 mg three times per day) compared to mesalazine suppositories (400 mg three times per day) in active UP. This study demonstrated that rectal 5-ASA was more effective than oral 5-ASA alone. According to physician global assessment, 83% (24/29) of patients receiving mesalazine suppositories were considered as “much improved” compared to 34% (10/29) of patients receiving mesalazine tablets ($p < 0.01$) [27]. A 2012 meta-analysis including patients with UC but not specifically UP, demonstrated no difference between oral and topical 5-ASA for induction of remission with a RR of 0.82 (95%CI: 0.52–1.28) for no remission with topical 5-ASA [28]. Regarding treatment formulation and dose of oral 5-ASA, evidence is in favor of 5-ASA granules rather than tablets in order to achieve clinical and endoscopic remission [29], and of a dose of at least 3.6 g of a pH-dependent release preparation rather than lower doses [30]. There are no dedicated studies comparing 5-ASA combination therapy with oral or topical therapies alone in UP. However, a double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal UC (disease extending < 50 cm from the anal verge) demonstrated that combination therapy was more effective than oral or topical 5-ASA alone [31].

Topical corticosteroids have also been demonstrated to induce clinical remission in distal UC [10,32]. However, regular treatment with prednisolone enemas, the most commonly used steroid, may produce side effects and hypothalamic pituitary adrenocortical suppression. Thus, beclomethasone dipropionate and budesonide, two corticosteroids with low systemic bioavailability, have been tested in patients with distal UC as enemas or foam [10]. A 2007 multicenter randomized double-bind trial demonstrated that beclomethasone dipropionate and mesalazine, both administered as enemas or foam, were as efficient to induce clinical and endoscopic remission at 4 weeks in 101 patients with distal UC (including proctitis and proctosigmoiditis) [33]. Recently, it was demonstrated in a multicenter, randomized, placebo-controlled trial ($n = 546$ patients with distal UC) that patients treated with budesonide rectal foam 2 mg/25 ml twice daily for 2 weeks, then once daily for 4 weeks had higher rate of clinical and endoscopic remission compared to patients treated with placebo (41% vs 24%, $p < 0.0001$) [34]. Previously, another study has shown that budesonide enemas were comparable to 5-ASA enemas in inducing remission [32]. In a 1997 meta-analysis, rectal 5-ASA was more effective than rectal corticosteroids for the induction of clinical and endoscopic remission (OR = 2.42; 95%CI: 1.72–3.41 and OR = 1.89; 95%CI: 1.29–2.76, respectively) [35]. Combination of topical beclomethasone dipropionate (3 mg) and mesalazine (2 g) enemas is more effective than either agent alone for induction of clinical and endoscopic remission [36]. In patients who fail to improve with topical and oral 5-ASA and topical corticosteroids, oral prednisolone should be tested even if no studies have evaluated its application specifically in proctitis.

The third European evidence-based ECCO consensus on the management of UC [17] states for the treatment of UP: “A mesalamine 1-g suppository once daily is the preferred initial treatment for mild or moderately active proctitis. Mesalamine foam or enemas are an alternative, but suppositories deliver the drug more effectively to the rectum and are better tolerated. Topical mesalamine is more effective than topical steroids. Combining topical mesalamine with oral mesalamine or topical steroids is more effective.”

The ECCO consensus also states that patients with endoscopically documented active proctitis, who fail oral corticosteroids combined with oral and rectal 5-ASA therapy, should be considered as having a refractory UP. Patients with steroid-dependent proctitis should also be included in the Definition of refractory UP. In patients with refractory UP, it is important to rule out alternative explanations of refractoriness such as poor adherence to prescribed therapy, inadequate delivery or concentration of the active drug, unrecognized complications (*Clostridium difficile* infection, proximal constipation …) and inappropriate diagnosis (rectal cancer, Crohn's disease, irritable bowel syndrome …). Therefore, before considering step-up therapy for patients with UP, physicians should review current symptoms, treatment history, and adherence to medical therapy. Intestinal infection with *C. difficile* or cytomegalovirus should be excluded using stool culture and PCR on serum and colonic biopsies. The activity of the disease should be assessed endoscopically and the appropriate use of conventional therapy should be reviewed. Attention should be focused on the formulation of topical therapy and whether it was used in conjunction with an adequate dose of oral therapy. After passing through all these steps, UC patients remaining with active UP should be considered for step-up therapy with available agents such as intravenous corticosteroids, azathioprine, *anti*-TNF or anticalcineurin (Fig. 1).

Please cite this article in press as: Pineton de Chambrun G, et al., Refractory ulcerative proctitis: How to treat it?, Best Practice & Research Clinical Gastroenterology (2018), https://doi.org/10.1016/j.bpg.2018.05.009