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When disease extent is not always a key parameter: Management of refractory ulcerative proctitis

Georgios Michalopoulos [a], Konstantinos Karmiris [b,*]

[a] Departments of Gastroenterology, Tzaneion General Hospital, Leoforos Afentouli, 18536, Piraeus, Greece
[b] Departments of Gastroenterology, Venizeleio General Hospital, Knosos Avenue, P.O.Box 44, 71409, Heraklion, Crete, Greece

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ABSTRACT

Background: Patients with ulcerative proctitis represent a sub-group of ulcerative colitis patients with specific characteristics. Disease-related symptoms, endoscopic findings and patient's personality perspectives create a difficult-to-assess condition in certain cases.

Objectives: To summarize available evidence on the management of refractory ulcerative proctitis and provide insights in treatment options.

Results: /Conclusion: Topical therapy plays a central role due to the location of the disease. However, well-established treatment options may become exhausted in a considerable proportion of ulcerative proctitis patients, indicating the need to advance to more potent therapies in order to induce and maintain clinical response and remission in these refractory cases. Systemic corticosteroids, thiopurines, calcineurin inhibitors, biologic agents and small molecules have all been tested with variable success rates. Investigational interventions as well as surgical procedures are kept as the ultimate resort in multi-treatment resistant cases. Identifying early prognostic factors that herald a disabling disease progression will help in optimizing treatment and avoiding surgery.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon, characterized by remitting and relapsing periods, affecting mainly young and middle aged patients and requiring lifelong treatment. The global incidence rate of UC varies between 0.5 and 24.5/100,000 person-years (Hochart et al., 2017; Moum et al., 1996; Solberg et al., 2009). UC may be limited to the rectum - proctitis (E1) or extended distally, left sided colitis (E2), or proximally, extensive colitis (E3), to the splenic flexure, a classification that affects treatment plan and optimal route of drug administration. (Silverberg et al., 2005).

Ulcerative proctitis (UP) is present in 25–55% of patients at diagnosis (Meucci et al., 2000) with the cumulative rate of relapse being 42%, 57% and 84% at 2, 5 and 10 years, respectively (Ayres et al., 1996; Bjornsson et al., 1998). Proximal extension of the disease may occur and is associated with a more severe clinical course and an increase in the risk of colorectal cancer. Cumulative rates of proximal extension reach 20%, 54% and 84% at 5, 10 and 20 years respectively, while almost 10% may show extension proximal to the splenic flexure (Henriksen et al., 2006). Risk factors associated with disease extension are: 1) disease severity at diagnosis as expressed by the endoscopic and total Mayo score, 2) need for corticosteroids at diagnosis, 3) chronic active and 4) chronic relapsing disease. (Kim et al., 2014). Successful treatment of UP may prevent or delay proximal extension (Pica et al., 2004).

UP follows an indolent course in the majority of patients with predominantly mild disease activity. However, symptoms can be very distressing and associated with a reduced quality of life despite appropriate therapeutic interventions. Typical symptoms of UP include loose stools, increased bowel frequency, rectal bleeding, tenesmus, urgency and incontinence as a consequence of chronic inflammation and scarring, resulting in a noncompliant rectum. Interestingly, a subset of patients may present with constipation (Meucci et al., 2000). Thus, timely and effective treatment of UP with potent therapies is not only important in controlling symptoms and improving quality of life but also in avoiding the risk of proximal disease progression and subsequent short-or long--term complications associated with this undesirable outcome.

The third European evidence-based ECCO consensus on the management of UC states that UP should be characterized as refractory when rectal and oral therapy with 5-aminosalicylates (5-ASAs) and corticosteroids (CS) have failed to induce and maintain remission (Harbord

Abbreviations: 5-ASAs, 5-aminosalicylates; CD, Crohn's disease; CS, Corticosteroids; IBD, inflammatory bowel disease; UC, ulcerative colitis; UP, ulcerative proctitis.

* Corresponding author.
E-mail addresses: gmicha78@hotmail.com (G. Michalopoulos), kkarmiris@gmail.com (K. Karmiris).

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et al., 2017). Refractory UP has also been defined as the absence of remission or improvement after two months of topical 5-ASAs treatment, with or without associated oral 5-ASAs and one month of topical CS (Peyrin-Biroulet et al., 2016). The incidence of refractory UP is estimated to be as high as 31% (Dubois et al., 2020). In this review article we will focus on the management of refractory UP.

2. Methods

The PubMed database and Cochrane library were searched to identify eligible studies reporting on the management of ulcerative proctitis. Both authors independently screened the databases with the following terms and the Boolean operators ('AND' or 'OR'): ('proctitis' OR 'ulcerative proctitis' OR 'refractory proctitis') AND ('treatment' OR 'management' OR 'therapy' OR 'surgery') with no time restriction to the query. The inclusion criteria were as follows: (i) confirmed diagnosis of UC; (ii) management of UP; (iii) human studies and (iv) studies published in English. The titles and abstracts were extracted and scrutinized and the full text of relevant publications was carefully revised to determine and evaluate available data. Manual search was also performed in the reference lists of the included studies to identify additional studies. Discrepancies in the data retrieved were resolved by consensus between the two authors. The names of the authors, year of publication, study design, duration of follow-up, intervention, treatment outcome and adverse events were captured.

3. Treatment of non-refractory disease

The cornerstone of treatment of active UP is based on rectally administered topical agents, which can directly act to the inflamed mucosa and have little systemic absorption minimizing potential side effects. Suppositories containing mesalazine seem to be more appropriate than enemas, since the maximum spread of enemas ranges from 11 to 40 cm from the anal verge and after 4 h only 40% of foam and 10% of liquid enemas can be detected in the rectum (van Bodegraven et al., 1996). Topical mesalazine treatment induced remission in 31–80% (median 67%) of patients with UP and left sided colitis in comparison to 7–11% in those who received placebo in a meta-analysis of 11 trials (Marshall and Irvine, 1995). A dose of 1 g of mesalazine suppository is considered as adequate for induction of remission of UP, with equal effectiveness when administered in a single daily dose or divided into two doses but better tolerance of the single dose (Gionchetti et al., 1997; Marteau and Florent, 2000; Lamet, 2011). There is no additive effect with doses over 1gr/day. A Japanese randomized, double blind, placebo controlled study showed that endoscopic remission rate was 83.8% in the mesalazine suppository versus 36.1% in the placebo arm ($p < 0.0001$) reinforcing the importance of mucosal healing as a therapeutic target. In line, rectal bleeding was significantly reduced already after the 3rd day of treatment, showing a very rapid treatment response (Watanabe et al., 2013).

Oral 5-ASAs monotherapy, although more convenient, seems to be inferior to topical monotherapy in UP (Gionchetti et al., 1998). The inferiority of oral monotherapy is most probably caused by limited exposure of the active substance to the distal colon due to proximal colonic stasis and rapid transit through the inflamed rectum (Hebden et al., 2000). Nevertheless, combination therapy with oral and topical 5-ASAs is superior to topical monotherapy and should be the choice in patients with active UP despite optimal treatment with topical therapy. This superiority is most probably attributed to the prolonged exposure of the rectum to the active substance in comparison to oral or topical mesalazine alone. (Frieri et al., 1999). So far, no study has investigated, whether the administration of combination therapy at baseline to all UP patients independently of disease severity and activity persistence is superior to topical therapy in decreasing the risk of proximal disease extension. Cost-effectiveness should also be included as an outcome measure in a study that will be designed to answer this question.

Topical mesalazine is also more effective than topical CS regimens (budesonide foam enema, beclomethasone dipropionate enemas etc) regarding symptomatic (odds ratio [OR] = 2.42, 95% CI = 1.72–3.41), endoscopic (OR = 1.89, 95% CI = 1.29–2.76), or histologic (OR = 2.03, 95% CI = 1.28–3.20) improvement (Marshall and Irvine, 1997). Combination of topical mesalazine and CS may exhibit better clinical, endoscopic and histologic results than either therapy alone. (Mulder et al., 1996). Oral systemic CS are administered in UP patients with persistent moderate to severe activity, where all possible combinations with the aforementioned formulations fail to induce remission. Maintenance of remission with orally and rectally administered 5-ASAs should be attempted, if remission is achieved (Harbord et al., 2017). It must be noted that although this approach is recommended for the treatment of UC, no studies have specifically evaluated its efficacy in UP. However, combination therapy could also offer benefit in preventing proximal extension of the disease in these patients with chronic active or frequently relapsing UP, who respond to oral CS. Nevertheless, some patients will not adequately respond to oral CS or will eventually develop CS dependency or exhibit already from the beginning of treatment CS refractoriness fulfilling the criteria for refractory disease and thus necessitating a step-up in therapy. But is the disease at this stage truly refractory?

Table 1
Reasons for treatment refractoriness in patients with ulcerative proctitis.

Etiology	Investigations	Approach
Lack of adherence to treatment	History, interview	Patient education, single vs divided doses, suppositories vs enemas, change route of administration
Suboptimal treatment (inadequate dose and schedule, monotherapy, increased BMI)		Dose optimization, combination therapy, supportive measures
Duration of treatment		Wait at least 2–3 weeks
Disease extension	Endoscopy	"Treat to target"
Proximal constipation	Abdominal x-ray	Non-stimulant osmotic laxatives
NSAIDS	History	Use of COX-2 inhibitors, alternative regimens
CMV	Biopsies (inclusion bodies, IHC, PCR)	Antiviral treatment
Clostridioides difficile	GDH, Toxins, NAAT	Treatment according to severity - guidelines
Superinfections (Cambylobacter, Salmonella, Shigella, Cryptosporidium, Strongyloides, Schistosoma)	Stool cultures for bacteria and parasites	Treat accordingly
STDs (Neisseria gonorrhoeae, *Chlamydia trachomatis*, Herpes simplex virus, Syphilis, Lymphogranuloma Venereum)	Cultures, PCR	Specific treatment as indicated
Crohn's disease	Ileocolonoscopy (repeat biopsies), MRE	Treatment modification
Radiotherapy or immunotherapy (cell-cycle checkpoint inhibitors) exposure	History, endoscopy	Treat accordingly
Mesalazine-induced colitis	Temporal association of symptoms	Treatment cessation and re-introduction trial
Proctitis cystica profunda, Chemical proctitis		

BMI: body mass index, CMV: cytomegalovirus, COX-2 inhibitors: cyclooxygenase-2 inhibitors, GDH: glutamate dehydrogenase, IGRA: interferon gamma release assay, IHC: immunohistochemistry, MRE: magnetic resonance enterography, NAAT: nucleic acid amplification tests, NSAIDs: non-steroidal anti-inflammatory drugs, PCR: polymerase chain reaction, STD: sexually transmitted diseases.

4. Treatment of refractory disease

4.1. Investigating reasons for refractoriness

Active disease should be documented using objective measures, including endoscopy and serum and fecal biomarkers in patients exhibiting symptoms and signs of refractoriness. The presence of inflammation will exclude functional gastrointestinal conditions, like irritable bowel syndrome, mucosal prolapse and pelvic floor dysfunction. Endoscopy will also serve to re-evaluate disease extension and exclude UP-related complications (strictures, malignancy).

Subsequently, alternative causes of disease refractoriness should be investigated prior to therapy escalation (Table 1). Risk factors that increase the probability of encountering refractory disease in due course are proximal disease extension, younger age at diagnosis, longer disease duration and male gender (Raine et al., 2021). Patient compliance is crucial for treatment success and must be evaluated in any case of inadequate response. Non-adherence to therapy has been reported in up to 38.9% of patients with IBD and seems to be independent of medication type or disease activity (Cervený et al., 2007). It has been shown that up to 70% of patients may stop mesalazine topical therapy even during the first month of treatment (Richter et al., 2012). It is easily understood that in patients with UP, topical treatment compliance has an even more crucial role and non-adherence can be avoided by good education of the patient aiming mainly at the significance and general safety of topical treatment. Modification of daily administration schedule and formulation of topical treatment may also help in terms of compliance since the increased volume and low viscosity of enemas may irritate some patients making it difficult for them to retain the drug for adequate time (van Bodegraven et al., 1996).

Treatment optimization is also of utmost importance. Up to 64% of UC patients may receive suboptimal doses of 5-ASAs and up to 75% of patients with distal colitis (E1 or E2) do not receive topical treatment (Reddy et al., 2005). It is important to escalate treatment from topical monotherapy to oral-topical combination with optimal doses (1 g/day topical and 4–4.8 g/day oral dosage according to compound in use) before considering more potent drugs and also wait at least 2–3 weeks before stepping-up to CS since mesalazine may require a prolonged period to achieve maximum effect (Orchard et al., 2011).

Disease extension, as noted before, may be associated with refractory symptoms and should be investigated thoroughly. Proximal constipation may also be associated with decreased treatment effectiveness and should always be considered in refractory cases. This is due to abnormal intestinal motility in patients with distal colitis that induces proximal colonic stasis. This stasis may affect drug delivery of oral formulations to the distal colon resulting in decreased drug concentrations in the inflamed area. This has been shown with scintigraphic methods in patients with active left sided colitis, where only 9% of labeled Eudragit-coated resin reached the distal colon, in comparison to 31% in healthy adults (Hebden et al., 2000). A plain abdominal x-ray may detect proximal stasis and in case of visible fecal impaction in the descending colon, administration of a non-stimulant osmotic laxative may increase 5-ASAs concentration in the diseased rectum.

Alternative diagnoses should also be excluded. Super-infections as well as other entities that may mimic or exacerbate UP should be ruled out. Special attention should be paid in cases with misdiagnosed Crohn's disease, mesalazine induced colitis, radiotherapy or immunotherapy (cell-cycle checkpoint inhibitors) exposure, proctitis cystica profunda or chemical proctitis (Table 1).

4.2. Treatment of refractory proctitis

Escalation and intensification of treatment should be the next step after careful history review and exclusion of all aforementioned causes of refractoriness in order to achieve remission and to decrease the risk of long term complications. Intravenous CS, thiopurines, biologics, JAK inhibitors and experimental drugs may all be used in these refractory cases leaving surgery as the last resort, if everything else fails. Most data originate from uncontrolled, retrospective, observational studies evaluating also these treatments in patients with more extensive disease. So, the quality of available evidence is in most cases low to very low and recommendations, where feasible, are considered weak.

4.2.1. Systemic corticosteroids

No studies have specifically evaluated systemic CS for the treatment of UP. In a study back in 1980s, patients with severe UC refractory to outpatient treatment with oral steroids and mesalazine received an intensive intravenous treatment with parenteral alimentation, 3 mg of β-methasone twice daily and antibiotics for at least 5 days. The remission rate was higher in patients with less extensive UC (88.2%) compared to those with pancolitis (46.8%, $p < 0.0025$) (Järnerot et al., 1985). In a more recent study, patients with severe UC extending at least to the splenic flexture were randomized to receive intravenously either 4 mg/kg/day cyclosporine or 40 mg/day methylprednisolone for 8 days. Response rate was 53% in the group of methylprednisolone (D'Haens et al., 2001). A plan for maintenance therapy should be designed at baseline, when intravenous CS are used to induce remission.

4.2.2. Thiopurines

Thiopurines were shown to be significantly superior to placebo in CS-dependent UC patients for maintaining CS free clinical and endoscopic remission (RR 0.68, 95% CI 0.54–0.86) but the overall quality of the evidence was rated as low mainly due to risk of bias and imprecision, while data were significantly heterogeneous when comparing thiopurines with 5-ASAs (Timmer et al., 2016). A recent large retrospective study investigating azathioprine monotherapy in 11928 IBD patients (UK IBD BioResource), including 379 with UP, showed that UP was associated with higher efficacy compared to more extensive disease (OR 1.56 vs extensive disease, 95% CI 1.23–1.98, $p = 0.0002$) without reporting response rates according to UC extent (Stournaras et al., 2021).

Azathioprine (2 mg/kg/day) was more effective than oral 5-ASAs (3.2 gr/day) in CS-dependent UC with 53% of patients receiving azathioprine versus 21% of those treated with 5-ASAs achieving steroid-free clinical and endoscopic remission after 6 months [OR 4.78, 95% CI 1.57–14.5]. However the study sample was small (36 patients in each arm) and only 8 patients (22%) in the azathioprine arm had distal UC (Ardizzone et al., 2006). Five out of 25 patients with refractory UP treated with azathioprine (median maximal dose of 2.2 [2.0–2.5] mg/kg/day), had a treatment success (defined as absence of colectomy, no need for anti-TNFalpha agents, inactive disease, ability to wean off CS and absence of azathioprine-related adverse events) after a median follow-up of 46.2 [26.4–47.8] months in a multicenter retrospective study (Mallet et al., 2017). Another retrospective study found that only 2/19 (11%) patients with refractory UP showed treatment success in the long term (defined as clinical response, no proximal disease extension, no need for systemic CS or treatment switch, absence of colectomy and endoscopic inactive disease, where available) to azathioprine monotherapy. This rate was significantly lower compared with the respective rate of treatment success in patients who received biologics (anti-TNFalpha, vedolizumab, 23/33, 70%, $p = 0.001$) (Dubois et al., 2020).

These results originating from very low quality of evidence mainly due to a small sample size and the retrospective uncontrolled study design indicate that azathioprine may have some effect in refractory UP but this effect is very limited in the long term. Thus, a clear recommendation about its use in this particular population cannot be made considering also the superior efficacy of alternative agents. .

4.2.3. Calcineurin inhibitors

Tacrolimus is a macrolide that inhibits activation of T-lymphocytes and has demonstrated its efficacy and safety in a randomized trial of refractory UC patients (Ogata et al., 2006). Wide use of tacrolimus is generally restricted due safety concerns and the need for measurement of

serum levels in case of systemic administration. However, topical administration through an enema or suppository formulation is an attractive alternative that may be associated with less toxicity (Kershner and Fitzsimmons, 1996).

The efficacy and safety of a galenic formulation of tacrolimus suppositories was investigated in a phase I trial of 12 patients with refractory UP. Clinical response (defined as a composite score containing clinical, endoscopic and histopathologic sub-scores measured at baseline and after 4 weeks of treatment) was shown in 10/12 (83%) patients. None of them reported side effects or developed laboratory disorders and blood trough levels of tacrolimus were too low to induce systemic immune suppression. (van Dieren et al., 2009).

An Australian 8-week double-blind, placebo-controlled study of administration of a galenic formulation of tacrolimus rectal ointment was conducted in the same period. The study was prematurely terminated due to ethical considerations because there were highly significant differences between the two arms in an interim analysis. Clinical response (defined as a reduction in the Mayo Clinic score of $\geq$3 points and a decrease of >30% from the baseline score, with a decrease of $\geq$1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1) was seen in 8/11 patients receiving rectal tacrolimus versus only 1/10 patients taking placebo (73% vs. 10%, $p = 0.004$). Furthermore, clinical remission (45% vs. 0%, $p = 0.015$) and mucosal healing (73% vs. 10%, $p = 0.004$) were also superior in favor of the tacrolimus arm. No safety issues were identified. (Lawrance et al., 2017). Tacrolimus suppositories were also administered in a retrospective study of 43 patients with distal colitis (the majority with UP). Overall, 60% (26/43) of the patients achieved clinical remission (Jaeger et al., 2019).

A recent randomized controlled, double-blind multicenter study including 85 patients with refractory UP showed no superiority of tacrolimus over beclomethasone suppositories. Specifically, the rates of clinical response (62.9% vs 59.5%, $p = 0.812$), clinical remission (45.7% vs 38.5%, $p = 0.638$), endoscopic response (67.6% vs 60%, $p = 0.636$) and endoscopic remission (29.7% vs 12.5%, $p = 0.092$) did not differ significantly between the tacrolimus and the beclomethasone group respectively. Concluding, the authors recommend tacrolimus local therapy as a reliable therapeutic option for refractory UP prior to step-up to thiopurines or biologicals (Lie, et al., 2020).

Low to moderate quality data indicate that tacrolimus is an effective and safe treatment at least short-term, when administered rectally in patients with refractory UP. However, the lack of long-term data and of a standardized drug formulation and dosage available in the market, evaluated in different research settings restrict its implementation in daily practice.

On the contrary, cyclosporine enemas in a dose of 350 mg/day were not superior to placebo in a randomized, double-blind, 4-week trial of 40 patients with mildly to moderately active left-sided UC refractory to oral and topical CS (an unknown number of patients with refractory UP was also included). Potential explanations for these negative results were the low dose or the infrequent dosing interval of cyclosporine, the delivery provided to the colonic mucosa by the water-based enema, the duration of treatment, disease refractoriness and the mixed population regarding disease extent (Sandborn et al., 1994).

4.2.4. Anti-TNFalpha agents

Infliximab, adalimumab and golimumab are the anti-TNFalpha agents approved for use in moderate to severe UC. ACT 1 and ACT 2 (two placebo-controlled, randomized trials) demonstrated that infliximab was superior to placebo in inducing and maintaining clinical response in patients with UC, but it must be noted that patients with UP were not included in these studies (Rutgeerts et al., 2005).

Limited data exist regarding the use of anti-TNFalpha agents in UP. A multicenter retrospective study concluded that 9/13 patients (69%) with UP, who received infliximab as induction therapy demonstrated complete (defined as absence of diarrhea and blood and CS sparing effect) and 2/13 (15%) partial (defined as marked clinical improvement but still persistent blood loss) short term clinical response. Furthermore, 9/11 responders (82%) maintained this response at last follow up (median: 17 months) and 4/7 patients with endoscopic re-evaluation demonstrated mucosal healing or mild endoscopic activity (Bouguen et al., 2010).

Short term clinical response and remission (defined as significant improvement and complete disappearance of UC-related symptoms respectively as judged by the treating physician) was seen in 80/104 (77%) and 52/104 (50%) patients treated with infliximab, adalimumab or golimumab in another nationwide retrospective study. Concomitant treatment with thiopurines at baseline was significantly associated with primary clinical remission. Among these 104 patients, the cumulative probability of sustained clinical remission was 87.6% $\pm$ 3.4% at 1 year, 74.7% $\pm$ 4.8% at 2 years, and 56.4% $\pm$ 6.2% at 5 years. A follow-up colonoscopy was available in 63/104 (61%) of patients after a median follow-up of 11.7 (IQR, 5.5–17.4) months. Among these patients, 60% (38/63) had mucosal healing (Mayo endoscopic subscore of 0 or 1). No difference in clinical efficacy was observed between the different anti-TNFalpha agents (Pineton de Chambrun et al., 2020).

In the previously mentioned retrospective study from Leuven, 26/33 patients with refractory UP received infliximab, adalimumab or golimumab and after a median follow up of 21 [IQR, 9–43] months 13/26 (50%) had treatment success (Dubois et al., 2020). Taken together these data suggest that anti-TNFalpha agents follow a similar pattern of efficacy in refractory UP as they do in more extensive UC (Rutgeerts et al., 2005) and that response rates are superior to those observed with azathioprine monotherapy. However, the quality of existing evidence is low originating from retrospective uncontrolled observational studies.

4.2.5. Non anti-TNFalpha biologics and small molecules

Vedolizumab induced and maintained remission in patients with moderate to severe UC in a randomized, double-blind, placebo-controlled trial (Gemini I). Disease should extend at least 15 cm from the anal verge in order for a patient to be enrolled. Thus, patients with UP were excluded (Feagan et al., 2013). However, there are indirect data regarding vedolizumab administration in refractory UP from two previously mentioned studies. In the study by Pineton de Chambrun et al. out of the 24 patients with primary non-response to anti-TNFalpha, 11/24 (46%) received vedolizumab and 9/11 (82%) achieved clinical remission. Moreover, 5/9 (56%) patients who finally received vedolizumab after secondary loss of response to anti-TNFalpha, achieved clinical remission. Thus the total response rate was 70% (14/20) (Pineton de Chambrun et al., 2020). Similarly, in the study by Dubois et al., 15 patients received vedolizumab (8 as first, 4 as second and 3 as third line biologic) and 67% (10/15) had treatment success within a median follow up of 11 [IQR 6–19] months (Dubois et al., 2020). These data imply that vedolizumab is an effective and safe option in the management of refractory UP, especially in patients failing anti-TNFalpha agents but again the quality of evidence is low also because of small sample size. Currently, there are no published studies reporting on the efficacy of tofacitinib or ustekinumab in UP.

4.2.6. Empirical and investigational therapeutic interventions

4.2.6.1. Acetarsol. Acetarsol is a pentavalent arsenic compound with antiprotozoal and antihelminthic properties. A double blind trial (20 patients in each arm) concluded that acetarsol suppositories are equally effective to prednisolone suppositories (Connell et al., 1965). Twenty-eight patients with refractory UP received acetarsol suppositories in a median (range) dose of 500 (500) mg and treatment duration of 74 (64) days in a retrospective study and 19/28 (67.9%) exhibited clinical response and 46.4% clinical remission. Over a median period of 6 (3) years, 6/28 patients experienced possible acetarsol-related adverse events (two patients had headache, one vomiting, one perianal pruritus and paraesthesia, one blepharitis and one sweating, palpitations and

weakness). All short-term side effects ceased at treatment withdrawal. No malignancy or long-term complications were reported (Argyriou et al., 2019). Another retrospective study of 39 patients with IBD and refractory proctitis (29 UC, 9 Crohn's disease and 1 indeterminate colitis) treated with acetarsol suppositories reported a 68% (26/39) clinical response rate (Kiely et al., 2018). Thus, acetarsol may have a role in the therapeutic algorithm of UP albeit the quality of existing data is considered very low.

4.2.6.2. Indigo naturalis. Indigo naturalis is a plant-derived blue pigment that has been used as a herbal medicine in many inflammatory diseases in traditional Chinese medicine. A 8-week, multicenter, randomized, double-blind, placebo-controlled Japanese study evaluated the efficacy and safety of 3 different doses of orally administered indigo naturalis in 86 patients with UC, including 19 with proctosigmoiditis. Clinical response was superior in the group of indigo naturalis [placebo: 13.6% (3/22), 0.5 g: 69.6% (16/23, $p = 0.0002$), 1.0 g: 75.0% (15/20, $p = 0.0001$), 2.0 g: 81.0% (17/21, $p < 0.0001$)]. However, serious adverse events including pulmonary arterial hypertension and intussusception have been reported raising long term safety issues (Naganuma et al., 2018). Indigo naturalis suppositories were administered in 10 UC patients with refractory proctitis despite treatment with 5-ASA and thiopurines in another Japanese 4-week, single-center, prospective, open-label study. The rates of clinical remission and mucosal healing were 30% (3/10) and 40% (4/10), respectively. No major side effects were encountered (Yoshimatsu et al., 2020).

4.2.6.3. Rebamipide. Rebamipide, is known to stimulate local prostaglandin synthesis and mucosal epithelial cell regeneration via an increase in the expression of epithelial growth factor and its receptor and has been studied in peptic ulcer disease. It has also been reported to exert an anti-inflammatory effect. (Zea-Iriarte et al., 1996). A Japanese open label prospective study investigated the efficacy and safety of twice daily rebamipide enemas administered for 4 weeks in 16 patients with UC including 4 patients with UP. Two UP patients with moderate severity at entry showed complete remission with no blood in stool and endoscopy revealed marked restoration of mucosal vascular patterns, while the other two were excluded due to lower than pre-defined compliance rate (Makiyama et al., 2005). Similar results were reported in 20 patients with UC and active proctosigmoiditis despite administration of prednisolone for 2 weeks, who received twice daily rebamipide enemas for 3 weeks (55% clinical remission, 80% endoscopic response) in another Japanese open label prospective study (Furuta et al., 2007). No major adverse events were reported in any of these studies. Nevertheless, despite these promising results no further studies have been conducted since 2007.

4.2.6.4. Alicaforsen. Alicaforsen is an antisense oligonucleotide agent that targets the messenger RNA for the production of human ICAM-1 receptor and is delivered topically in an enema form. A meta-analysis of 4 phase II studies concluded that nightly alicaforsen 240 mg in 60 ml enema for 6 weeks performed better than placebo in UC patients with limited distal disease (up to 40 cm from the anal verge) and/or moderate or severe activity (% decrease of disease activity index, week 6, 49.3% vs. 6.9%, $p < 0.05$ and week 10, 51.9% vs. 16.5%, $p < 0.1$). Durable response beyond 30 weeks of treatment was also shown compared to mesalazine enemas (39.6% vs. 18.6%, $p < 0.049$) (Vegter et al., 2013). No alarming side effects were reported. Therefore, moderate quality data indicate that rectally administered alicaforsen may represent an effective and well-tolerated alternative to the standard of care in clinical practice for patients with distal UC although the efficacy of the enema formulation in refractory UP is questionable.

4.2.6.5. Sacral nerve stimulation. Sacral nerve stimulation is a mini-invasive procedure that has been used to treat fecal incontinence (Jarrett et al., 2004). Additionally, there are data that imply that sacral nerve stimulation may decrease intestinal epithelial barrier permeability, which has a key role in the pathogenesis of UC (Provost et al., 2015). Clinical, endoscopic and histologic response after initiation of sacral nerve stimulation was reported in a patient with refractory UP (under combination treatment with infliximab and methotrexate), treated for fecal incontinence. This effect was sustained for at least 18 months (implantation of a permanent neuromodulator) (Brégeon et al., 2015). This approach is attractive, since it is not based on immunosuppression, although it has been tested in only one case.

4.2.6.6. Appendectomy. This approach is mainly based on the inverse association that has been found in the risk of acquiring UC in patients operated for an inflammatory condition (appendicitis or lymphadenitis) and especially those younger than 20 years old (Andersson et al., 2001). Appendectomy was performed in 30 non-smoking patients with refractory UP without a history suggestive of previous appendicitis or mesenteric adenitis in a prospective case series. Twenty-nine of the 30 appendices removed (97%) were macroscopically normal with histologic examination revealing ulcerative appendicitis in 16/30 (53%) cases and no signs typical of acute appendicitis in any of the patients. Twenty seven out of thirty patients (90%) achieved an improvement in the Simple Clinical Colitis Activity Index and 12/30 (40%) experienced resolution of all symptoms for a median of 9 (range 6–25) months, such that all previous pharmacological treatments could be withdrawn. Appendiceal histology could not predict which of the patients might benefit from appendicectomy (Bolin et al., 2009).

Similarly, 8 patients with UP refractory only to combined oral and topical mesalazine underwent elective appendectomy and all of them achieved mucosal healing in a median follow up of 3.6 years. All patients had histologic findings compatible with acute appendicitis (Bageacu et al., 2011). Laparoscopic appendicectomy was also offered as an alternative to colectomy in 28 patients with therapy refractory UC, including 6 with UP in a multicenter, prospective study. Three months later, 14/28 patients had a clinical response and 7/28 achieved endoscopic remission. After a median follow-up of 3.7 (range 2.3–5.2) years, 13/27 patients had a sustained clinical response (Stellingwerf et al., 2019). Pathological evaluation was possible in 28 patients. After a median of 13.0 weeks (range 7–51), pathological response was seen in 13 patients (46%). Appendiceal inflammation was highly predictive of pathological response when compared with no inflammation or extensive ulcerations (85% vs 20%, $p = 0.001$) (Sahami et al., 2019).

Appendectomy after UC diagnosis was associated with a lower colectomy rate compared to no appendectomy (HR 0.16, 95% CI 0.04–0.66, $p = 0.011$) and delayed colectomy in a recent retrospective, multicenter cohort study of 826 UC patients. No significant differences were found in colorectal cancer rate between patients with and without appendectomy (1.6% versus 1.2%, $p = 0.555$) (Stellingwerf et al., 2021). Thus, elective appendicectomy may be offered as an alternative to immunosuppressants or proctocolectomy in selected cases with refractory UP.

4.2.7. Surgery

Surgery is the last resort for treating refractory UP and is considered as a «treatment failure» among gastroenterologists. The 20-year cumulative colectomy rate was 7.6% (95% CI: 5.4–9.8) in patients with UP in a well-characterized Norwegian inception cohort (Monstad et al., 2021). The procedure of choice is total proctocolectomy with ileal pouch anal anastomosis or with end ileostomy (Øresland et al., 2015). In the cohort of patients with refractory UP treated with azathioprine, 3/25 patients (12%) ultimately underwent proctocolectomy (Mallet et al., 2017). Restorative proctocolectomy with ileal pouch anal anastomosis was performed in 27/263 (10.3%) patients with refractory distal colitis in a retrospective cohort study. No late complications were observed after a median follow-up of 35 months (range 14–109). A significant improvement in fecal incontinence and a decrease in daytime and nocturnal stool

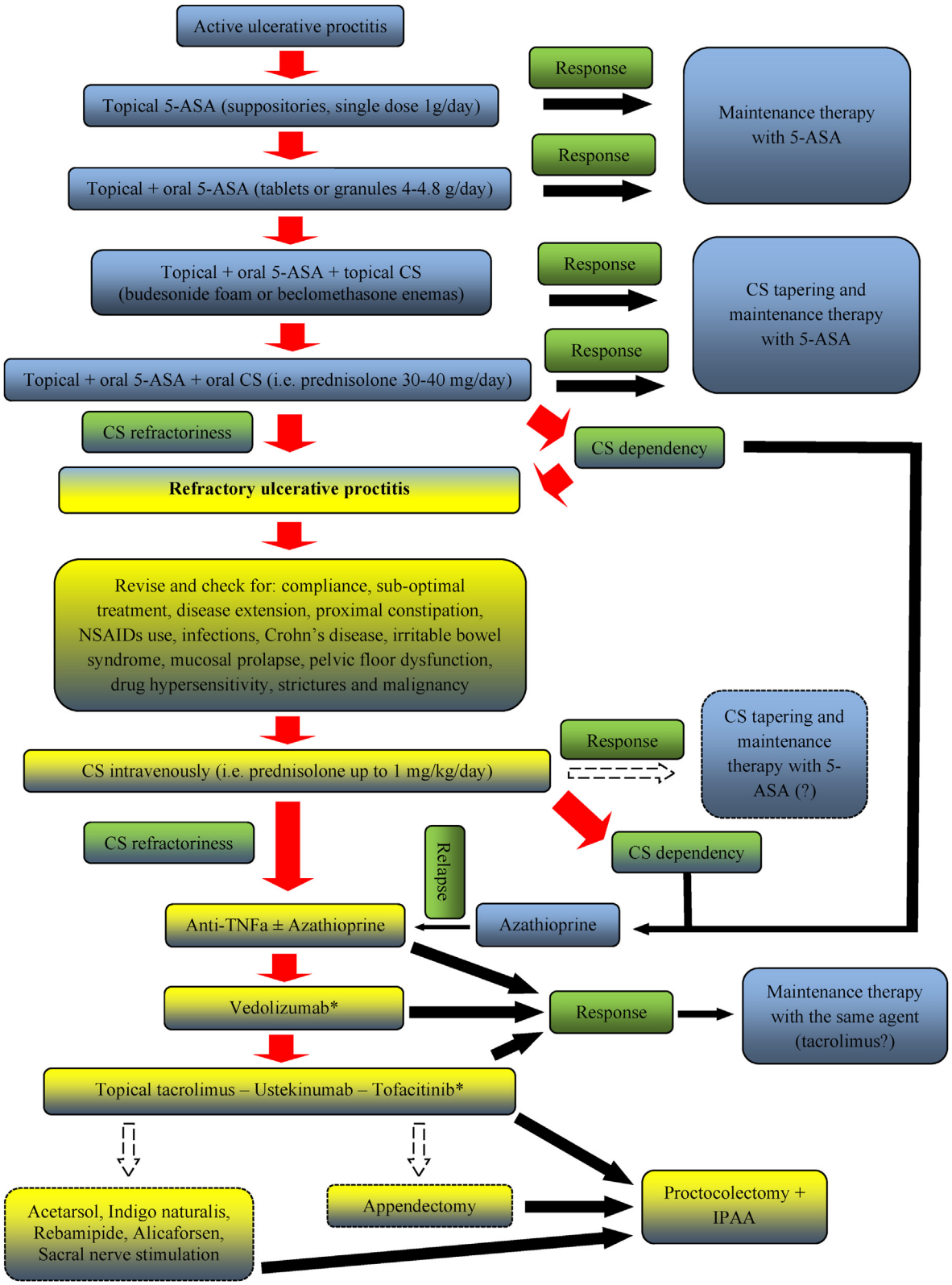

Fig. 1. Treatment algorithm of refractory ulcerative proctitis.
5-ASA, 5-aminosalicylates; IPAA, ileal-pouch anal anastomosis; NSAIDS, non-steroidal anti-inflammatory drugs,
Dashed arrows and box lining: limited evidence
* these steps can mutually change based on evidence for more extensive UC, UP specific profile characteristics, safety issues, treating physician's or patient's preference or local reimbursement policy.

frequency was observed in the majority of patients. The majority (25/27, 93%) were satisfied with the outcome of the procedure and wished that they had undergone the operation earlier during the disease course (Brunel et al., 1999).

Most patients with UP don't have systemic symptoms and some of them even learn to tolerate their chronic UP-related manifestations being reluctant in undergoing a surgical procedure with a possibility of acquiring a permanent stoma in case of pouch failure and decide to try less well-validated treatment options. However, restorative proctocolectomy with ileal pouch anal anastomosis remains a valid option with good results and clear improvement of quality of life.

5. Discussion

Refractory UP has emerged as a demanding clinical scenario, affecting a considerable percentage of UP patients. Few studies have investigated the impact of UC treatment exclusively in patients with UP since most of them have enrolled a mixed population comprising of patients with left sided colitis and UP or even excluded patients with UP despite its high prevalence even at UC diagnosis. On the other hand, UP patients can present with very distressing symptoms, poor quality of life and severe endoscopic lesions accumulating a significant burden on the basis of a unique profile. Thus, the management of these patients can become very challenging, since there is predominantly very low to low level of evidence for the majority of current treatments, due to small sample size in studies conducted and the exclusion of UP patients from randomized controlled trials designed to evaluate the efficacy and safety of a new agent in UC. Ideally, the treatment of refractory UP requires the engagement of a multidisciplinary team. Fig. 1 depicts an algorithm for treating refractory UP patients based on current knowledge.

A problem that clinicians confront is that there is no globally established definition for refractory UP. Several attempts have been taken to define refractory UC, in general. A disease not responding to or losing response to all classes of licensed immunosuppressive and biologic agents has been suggested as a definition in a recent Consensus Topical Review (Raine et al., 2021). Refractory UC was defined as active disease despite adequate therapeutic trials of 5ASAs, CS, immunomodulators, and approved biologics in a study of appendectomy as a salvage intervention prior to proctocolectomy (Sahami et al., 2019). The establishment of a universally accepted and adopted definition of refractory UP, applied in different populations, will help in performing large scale clinical studies and in including these patients in the design of pharmaceutical trials.

The identification of risk factors for a disabling disease course of UP could aid clinicians in accelerating the step-up treatment algorithm. Recently, histologic inflammation in the endoscopically uninflamed mucosa at the time of diagnosis was associated with worse outcomes in limited UC and especially disease complications, including colectomy (adjusted hazard ratio, 4.79; 95% confidence interval, 1.10–20.9; $p = 0.04$) (de Frias Gomes et al., 2021). Younger age at diagnosis (HR 0.98, 95% CI 0.96–0.99) and continuous active disease (HR 2.18, 95% CI 1.27–3.73) were identified as independent risk factors for proximal disease extension in a single center historical cohort of incident UC cases (Sahami et al., 2017). Timely recognition of these factors will aid decision making in treating patients with refractory UP.

In conclusion, patients with UP comprise a sub-group with certain particular characteristics that differ them from those with more extensive UC. The goal of inducing and maintaining clinical and endoscopic remission is largely based on topical therapeutic options frequently combined with oral regimens. Several available agents for the treatment of UC are offered for managing refractory UP as well. Investigational interventions and surgery will be needed in persistently active disease, despite administration of the aforementioned therapies in order to restore remission and improve quality of life. There is an urgent need for randomized controlled trials in patients with UP in order to gain more solid evidence regarding efficacy and safety of available therapies and to tailor current treatment algorithms for more extensive UC.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GM has received speaker and/or consultant and/or advisory board member fees from Abbvie, Amgen, Ferring, Genesis, Janssen, MSD, Pfizer and Takeda; KK has received speaker and/or consultant and/or advisory board member fees from Abbvie, Aenorasis, Amgen, Ferring, Galenica, Genesis, Janssen, MSD, Pfizer and Takeda.

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