

EXPERT OPINION

1. Introduction
2. Management of ulcerative proctitis
3. Re-evaluation
5. Surgery
6. Maintenance treatment
7. Colorectal cancer risk and surveillance
8. Expert opinion

Ulcerative proctitis: an update on the pharmacotherapy and management

Krisztina B Gecse & Peter L Lakatos[†]

[†]*Semmelweis University, 1st Department of Medicine, Budapest, Hungary*

Introduction: Ulcerative colitis (UC) presents as proctitis in approximately a quarter of the patients. It may progress into left-sided or extensive colitis in up to 50% of cases upon long-term follow-up.

Areas covered: Currently available data on ulcerative proctitis are summarized and critically reviewed. Extensive literature search (MEDLINE) was performed to identify relevant articles up to March 2014.

Expert opinion: The short-term goal of the treatment in UC is to induce remission, whereas long-term goals are to maintain remission and prevent disease progression. Topically administered 5-aminosalicylates (5-ASA) and corticosteroids are effective in the treatment of proctitis, although they seem to be underused in everyday practice. Locally administered 5-ASA preparations are more effective than oral compounds. The combination of topical and oral 5-ASA and steroids should be considered for escalation of treatment. Refractory patients should be re-evaluated to exclude for compliance failures, infections or proximal disease extent. True refractory or steroid-dependent patients may require immunomodulators or biological therapy. Alternative medicine can be used complementarily, while experimental approaches are reserved for patients failing conventional medication. Proctocolectomy may be the last resort of treatment. Upon long-term, 5-ASA maintenance treatment is indicated in all UC cases to prevent relapse and disease progression.

Keywords: azathioprine, infliximab, steroids, therapy, ulcerative colitis, ulcerative proctitis, 5-aminosalicylates

Expert Opin. Pharmacother. [Early Online]

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main types of chronic inflammatory bowel diseases (IBD). UC is considered to develop due to a dysregulated immune response against the commensal gut microflora in a genetically predisposed individual [1]. Although, the precise trigger of the disease is unknown, the common final pathway is a vicious circle of mucosal inflammation and disrupted epithelial barrier function [1]. UC is characterized by colonic inflammation limited to the mucosa. It typically involves the rectum and may extend proximally in a continuous fashion. Depending on disease extent, UC can be classified as proctitis (E1, inflammation limited to the rectum), left-sided colitis (E2, inflammation terminating at the splenic flexure) or extensive colitis (E3) according to the Montreal classification [2]. However, some patients with proctitis or left-sided colitis may also exhibit a caecal patch of inflammation [3].

Incidence rates for UC vary from 0.5 to 24.5 per 100,000 person-years worldwide [4]. Approximately, a quarter of UC patients present with proctitis at the time of diagnosis [5]. In comparison, left-sided colitis is the initial diagnosis in half of the patients and extensive colitis in another quarter of the patients [5]. Importantly, upon 5-year follow-up proximal extension of ulcerative proctitis (UP) may

informa
healthcare

Article highlights.

- The short-term goal of treatment in proctitis is to induce remission, whereas long-term goals are to maintain remission and prevent disease progression.
- In mild proctitis topical 5-ASA, in moderate-to-severe proctitis a combination of oral and topical 5-ASA preparations are considered as first-line treatment. In severe proctitis, topical and oral corticosteroids should be considered additionally.
- Patients refractory to combined topical and systemic 5-ASA and steroid therapy should be reinvestigated for other causes of therapeutic failure. In true refractory patients escalation of treatment to thiopurines and anti-TNF can be recommended.
- Proctocolectomy with ileal pouch anal anastomosis is considered as the last resort of treatment.
- Long-term maintenance therapy is recommended. The choice of maintenance treatment (topical and/or oral 5-ASA, thiopurines or anti-TNF) depends on previous disease severity and response to treatment.

This box summarises key points contained in the article.

occur in 20 – 28% of the patients, with 4 – 10% progressing to extensive colitis [6,7]. Long-term epidemiological studies show that up to half of the proctitis patients exhibit proximal disease extension 10 years after diagnosis [7-10]. Furthermore, the probability for disease progression was 53% upon 25 years of patients' follow-up [9]. Increased disease severity upon diagnosis, as indicated by both the endoscopic and total Mayo score, and corticosteroid use were associated with disease extension. Additionally, chronic, continuous and relapsing disease courses were also related to extension of mucosal inflammation [8]. Evidence suggests that prolonged oral mesalazine treatment may prevent proximal spread of rectal inflammation, while topical therapy prevents disease relapse [11,12]. Therefore, while the short-term goal of treatment in proctitis is to induce remission, long-term goals are to maintain remission and prevent disease progression.

This article aims to review and evaluate available data on the management of UP. Of note, only few data are available exclusively on the treatment of UP. Studies usually include patients with proctitis and distal colitis without clear distinction between the two subgroups [13]. In addition, patients with proctitis only were excluded from biological studies focusing on UC, such as the ULTRA trial on adalimumab, the PURSUIT trials on golimumab or the GEMINI trial on vedolizumab [14-17].

2. Management of ulcerative proctitis

2.1 Active proctitis

2.1.1 Formulation and delivery

Rectally administered topical agents represent the first-line therapeutic option in proctitis, as they directly target the site of inflammation when sufficient contact time is allowed to

reach effective mucosal drug concentration. In addition, side effects are uncommon, as they are rarely associated with significant serum concentrations. Drug formulations such as suppository, foam and enema enable optimized delivery to the affected mucosa. Suppositories seem to be more appropriate than enemas in the treatment of proctitis, as although the latter may reach the splenic flexure, its maximum spread is localized from 11 to 40 cm from the anal verge [18,19]. Liquid and foam mesalazine enemas seem to be equally effective in the treatment of left-sided colitis and proctitis [20].

Delivery systems of oral 5-aminosalicylate (5-ASA) compounds can be divided into azo-compounds, controlled release, pH-dependent (either pH6 or pH7) and composite (pH-dependent combined with controlled release) types [21]. Although data are abundant on different delivery systems, yet evidence for difference in efficacy is weak.

2.1.2 5-Aminosalicylates

Topical 5-ASA-induced remission in active proctitis and distal colitis was 31 – 80% (median 67%) compared with 7 – 11% in patients given placebo in a meta-analysis of 11 trials including 778 patients [22]. Single dose of mesalazine suppository 1 g daily was shown to be equally effective and better tolerated than mesalazine 500 mg suppository twice (b.i.d.) or thrice daily (t.i.d.) [23,24]. Daily dose of 1 g mesalazine suppository seems optimal, and no dose response has been observed with regard to topical treatment [25]. According to a recent multi-centre, randomized, double-blind, placebo-controlled study, endoscopic remission rates after 4 weeks of treatment with 1 g mesalazine or placebo suppository were 83.8% versus 36.1% ($p < 0.0001$) [26]. The percentage of patients without rectal bleeding was significantly higher already after the third day of treatment [26]. In comparison with topical steroids, topical mesalazine proved to be more effective in terms of clinical symptoms (OR = 2.42, 95%CI: 1.72 – 3.41), endoscopy (OR = 1.89, 95%CI: 1.29 – 2.76) or histology (OR = 2.03, 95%CI: 1.28 – 3.20) [27].

Oral 5-ASAs are less effective than topical 5-ASAs in treating proctitis, which may be due to the rapid transit and decreased contact time with the inflamed mucosa, and the relatively low concentration of the drug reaching the rectum [28,29]. However, oral 5-ASAs seem to be associated with better patient compliance. A recent Cochrane review showed that mesalazine exhibits the same therapeutic benefit in UC as its prodrug, sulfasalazine, in inducing remission and is better tolerated by patients [30]. The rate of adverse events was 29% in the sulfasalazine-treated patients compared with 15% in the mesalazine-treated patients (relative risk 0.48, 95% CI 0.37 – 0.63) [30]. Sulfasalazine is associated with side effects such as nausea, vomiting, abdominal pain, fever, skin rash, neutropenia, male infertility, folate deficiency, neuropathy, autoimmune haemolysis and rarely with nephrotoxicity, hepatotoxicity or pancreatitis. Once-daily dosing of 5-ASA (2 g/day) was shown to be as efficacious as conventional dosing and may also result in improved adherence [30,31]. In

mild-to-moderate UC, 2.4 g/day of delayed release oral mesalazine (Asacol) appeared effective for induction. However, patients with moderate disease activity may benefit from a higher dose of 4.8 g as shown by the ASCEND trials [32-34].

There have been no dedicated trials to evaluate combination therapy of topical and oral mesalazine in proctitis. However, combination therapy induces faster relief of symptoms and significantly greater change in the Disease Activity Index than either topical or oral mesalazine alone for colitis extending no more than 50 cm from the anal verge [35].

2.1.3 Corticosteroids

Rectally administered corticosteroids are also effective in inducing remission in UP [36]. Rapidly metabolizing corticosteroids with low systemic bioavailability result in reduced adrenal suppression compared to prednisolone enemas [37]. Budesonide enemas were significantly more effective than placebo and comparable to 5-ASA enemas in inducing remission [36,38]. Other high glucocorticoid potency and low bioavailability steroids, such as beclomethasone dipropionate enemas showed similar efficacy to prednisolone and to topically administered 5-ASA in improving the symptoms and inducing remission [37,39].

Combination of topical mesalazine and steroid treatment may be of benefit. Beclomethasone dipropionate (3 mg) and mesalazine (2 g) enemas produced significantly better clinical, endoscopic and histological results than either agent alone [40]. Patients who fail to improve on a combination therapy of topical and oral 5-ASA and topical corticosteroids should be treated with oral prednisolone (40 mg/day for 1 week, reducing 5 mg/day every week) [41-43]. In patients with persisting active UC after oral steroid and 5-ASA treatment, remission was achieved within a week in 90%, by intensive intravenous steroid treatment [44]. Methylprednisolone 60 mg/24 h or hydrocortisone 100 mg four times daily are used as intravenous corticosteroids for a maximum of 7 – 10 days [43]. Although systemic corticosteroids have been widely used in the treatment of UC for the past 60 years, no studies evaluated their application in proctitis.

Interestingly, despite all convincing evidence for topical treatment of proctitis, it seems to be underused in everyday practice. In a Swiss cohort, only 39% of patients received topical therapy with 5-ASA or corticosteroids either in monotherapy or in combination with systemic treatment for remission induction [45].

3. Re-evaluation

In patients who fail to respond to topical and systemic 5-ASA and topical and oral corticosteroids, alternative causes of therapy failures should be investigated prior to escalation of therapy. Non-adherence to therapy was reported by 38.9% of IBD patients and was irrespective of medication type or disease activity [46]. Colitis due to hypersensitivity to 5-ASA may also mimic a flare and is difficult to distinguish. Proximal

disease extension and superinfections predisposing to that, such as *Clostridium difficile* and cytomegalovirus (CMV) should be ruled out. Alternative explanations may also include inappropriate diagnosis, such as irritable bowel syndrome, CD, mucosal prolapse or cancer. Other rare causes including proctitis cystica profunda or sexually transmitted infections, such as herpetic, gonococcal or syphilitic proctitis should also be considered.

4 True therapy-refractory and steroid-dependent proctitis

True therapy-refractory cases can be extremely challenging to manage. Options mainly include thiopurines and anti-TNF agents. Salvage medical therapies may also include intravenous or oral cyclosporine or oral or rectal tacrolimus [47]. If not acutely ill, the patient may benefit from alternative therapies, whose efficacy is based on small open-label trials.

4.1 Thiopurines

There are no prospective dedicated trials to evaluate the effect of thiopurines in UC. A recent retrospective study, however, indicated that in steroid-dependent patients administration of azathioprine (AZA) resulted in significantly higher therapeutic success (71.2%) compared to patients with AZA intolerance (25.0%, $p < 0.001$) upon long-term follow-up [48]. Additionally, a recent trial randomized moderate-to-severe UC patients to receive AZA (2.5 mg/kg), infliximab (regular dosing regimen) or AZA and infliximab combination therapy. Corticosteroid-free remission at week 16 was achieved by 39.7% of patients receiving combination therapy compared with 22.1% receiving infliximab ($p = 0.017$) and 23.7% receiving AZA monotherapy ($p = 0.032$) [49].

4.2 Anti-TNF

In the ACT 1 and 2 trials on infliximab, 55% of patients had left-sided or distal colitis [13]. Although no separate subgroup analysis was carried out, two-thirds of UC patients failing 5-ASAs, steroids or thiopurines responded to regular infliximab dosing regimen [13]. A recent small retrospective cohort focusing on the efficacy of infliximab in therapy-refractory proctitis patients showed that infliximab-induced clinical response in 69% and remission in about 30% of patients [50]. Notably, patients with UP were excluded from most anti-TNF prospective randomized controlled trials [14-17]. Therefore, currently infliximab has the most available evidence on anti-TNF treatment of proctitis.

4.3 Salvage therapy

Intravenous cyclosporine (2 – 4 mg/kg/d) is also effective in patients failing intravenous corticosteroids; however, its use is limited by side effects [47]. Cyclosporine enema was not more efficient than placebo in active left-sided colitis [51]. Two pilot studies evaluated the effect of locally administered tacrolimus ointment, suppository or enema in UP and distal

colitis [52,53]. Two-thirds of the patients had clinical improvement after 4 – 8 weeks of topical tacrolimus treatment. In a large retrospective chart review, which included 18 patients with proctitis, oral tacrolimus was efficient in steroid-refractory cases [54]. However, in contrast to potential toxicity of systemic administration, tacrolimus trough levels were low after local administration and side effects were reported by none of the patients [53]. Topically administered infliximab was also shown to be effective in a refractory case previously unresponsive to intravenous induction treatment [55].

4.4 Experimental treatment

Rebamipide, an agent suppressing neutrophil function and stimulating epithelial cell regeneration, induced significant clinical, endoscopic and histological improvement when administered as enemas in patients with proctitis or distal colitis [56]. Case series have shown that elective appendectomy can be associated with clinical improvement or complete resolution of symptoms [57,58]. Additionally, several topical agents have been investigated, such as epidermal growth factor, ecabet sodium, butyrate, arsenic, ropivacaine, bismuth subsalicylate and thromboxane [59-61]. Although some of these agents show encouraging preliminary results, most compounds were not evaluated in greater patient numbers, and therefore, solid evidence is still lacking to suggest their use in everyday practice.

4.5 Complementary and alternative medicine

Complementary alternative medicine (CAM) has been popular by tradition in Asia [62]. In a recent systematic review including 14 trials on UC, aloe vera gel, *Triticum aestivum* (wheat grass juice), *Andrographis paniculata* extract (HMPL-004) and topical Xilei San (a Chinese herbal medicine with anti-inflammatory effect) were superior to placebo in inducing remission or response [63]. Additionally, curcumin was superior to placebo in maintaining remission, while *Boswellia serrata* gum resin and *Plantago ovata* seeds were as effective as mesalazine [64]. Although initial results with CAM seem to be encouraging, further trials are needed to confirm their efficacy in large patient numbers and to encourage their use in daily practice.

5. Surgery

Colectomy in proctitis (without disease extension) is considered in exceptional cases. The outcome of total proctocolectomy with ileal pouch anal anastomosis (IPAA) formation is good. In 263 patients who had a restorative proctocolectomy, 27 patients had surgery for distal disease and all but one patient were satisfied with the results and most patients wished that they had had surgery sooner [65]. However, complications, such as cuffitis may develop, where rectal bleeding is a characteristic feature. Mesalazine suppository 500 mg b.i.d. was effective in reducing clinical, endoscopic and histological activity in cuffitis [66]. A recent cohort examined the long-term course

of cuffitis in patients after IPAA. After a median follow-up of 6 years, 33.3% of patients had 5-ASA/steroid-responsive cuffitis. In patients with 5-ASA/steroid-dependent or -refractory cuffitis, 32.8% was diagnosed with CD of the pouch and 24.1% had surgical complications [67].

6. Maintenance treatment

Only a small percentage of patients are able to discontinue long-term therapy without disease relapse. As disease extension and relapse can be prevented by maintenance therapy, patients are encouraged to adhere to maintenance therapy. The length of the recommended maintenance therapy in patients with long-term clinical remission is, however, conflictive. Of note, data from a US database showed that maintenance therapy is not continued in the majority of proctitis cases. Seventy per cent of UP patients who were initially treated with mesalazine suppositories, and even 40 – 50% of those patients who began oral or systemic glucocorticosteroid, did not take further medication after remission induction [68].

Traditionally, oral 5-ASA and sulfasalazine were used for maintenance treatment in UC. A recent Cochrane review reported that sulfasalazine was superior in the maintenance setting [69]. A recent meta-analysis including seven randomized-controlled trials (n = 555 patients) showed that topical mesalazine was effective in preventing relapse of distal UC [12,70]. In the study, 500 mg mesalazine b.i.d. seems to be the most efficient therapeutic regimen for maintenance with a cumulative relapse rate of 10% at 12 months (95% CI: 0 – 21) [71]. However, even intermittent topical treatment is more efficient maintenance treatment than placebo [72,73].

There are no dedicated studies to evaluate the efficacy of rectally administered corticosteroids for the maintenance treatment in proctitis. In the only randomized placebo-controlled trial, oral prednisone was ineffective in maintaining the remission induced by oral steroids at 6 months [74]. More importantly, cumulative doses may be associated with well-known steroid side effects.

Clinical trials showed benefit from thiopurine treatment in UC maintenance [75]. The 1-year relapse rates were significantly lower in patients taking AZA (36%) compared with placebo (59%, $p = 0.04$) [76]. In a recent randomized clinical trial, steroid-dependent UC patients treated with AZA (2 mg/kg/d) had a significantly higher rate of clinical and endoscopic remission, leading to steroids withdrawal in a greater percentage of cases compared with patients receiving only high-dose oral 5-ASA (53 vs 19%, $p = 0.006$) [77]. Finally, a randomized study suggests a favourable role of probiotics, which was comparable to mesalazine in the maintenance treatment in UC [78].

7. Colorectal cancer risk and surveillance

Longstanding UC is associated with increased colorectal cancer (CRC) risk. Although risks estimates vary, it is

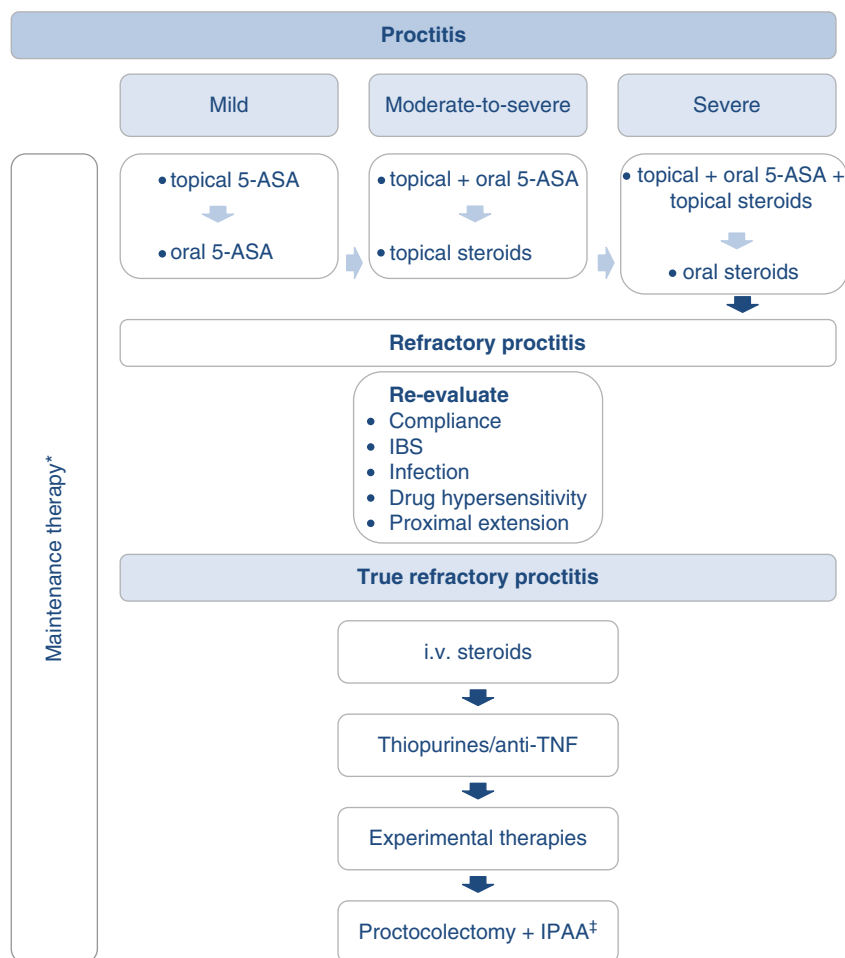


Figure 1. Treatment algorithm for patients with ulcerative proctitis.

*Depends on disease severity, induction agent and previous disease course: topical (or the combination of topical and oral) 5-ASA is recommended as first-line, immunosuppressives should be considered in steroid dependent cases, while immunosuppressives/anti-TNFs are recommended in refractory cases.

‡Considered in exceptional cases.

5-ASA: 5-Aminosalicylates; IBS: Irritable bowel syndrome; IPAA: ileo-anal pouch anastomosis; i.v.: intravenous.

associated with the extent, duration and severity of mucosal inflammation. A systematic review from the previous decade reported a cumulative CRC risk of 2% at 10 years, 8% at 20 years and 18% at 30 years [79]. In contrast, in a most recent meta-analysis, the cumulative CRC risk was < 1% at 10 years, 0.4 – 2% at 15 years and 1.1 – 5.3% at 20 years [80]. The reason behind the changing trend could be multifactorial including increased surveillance, changing treatment goals (full mucosal healing) and possible chemopreventive effects of 5-ASA. A recent review on 5-ASA concluded that the ability to heal colonic mucosa as well as influencing molecular pathways of carcinogenesis may contribute to possible chemoprevention [81]. With regard to disease limited to the rectum, no increased CRC risk is reported. Therefore, according to the recent ECCO guidelines after screening colonoscopy at 6 – 8 years after the onset of symptoms, inclusion in a regular surveillance colonoscopy program is not recommended in patients without proximal extension [82].

8. Expert opinion

The short-term goal of treatment in proctitis is to induce remission, whereas long-term goals are to maintain remission and prevent disease progression (Figure 1). The first-line therapy for active proctitis should be topical 5-ASA in line with the results from meta-analyses of published trials show that topical 5-ASA is superior to placebo and conventional corticosteroids in inducing remission. One gram once daily dosing of 5-ASA suppository has been shown to be equally effective and better tolerated than b.i.d. or t.i.d. suppository. Short-term remission rates may be as high as 85%. In case of suboptimal therapeutic response to topical 5-ASA, treatment can be extended with oral 5-ASA and/or topical steroids, as the combination of rectal 5-ASA with a rectal corticosteroid or oral aminosalicylate is superior to rectal 5-ASA alone [83]. Rectally administered corticosteroid therapy with suppositories or

foam is an effective alternative for patients intolerant of or unresponsive to 5-ASA.

In moderate-to-severe UP, a combination of oral and topical 5-ASA-based therapy should be considered as first-line treatment. In severe UP, oral or intravenous corticosteroids should be applied (at a maximum dose of prednisolone 40 – 60 mg, or the equivalent of methylprednisolone).

Refractory proctitis represents a difficult clinical entity for both patients and doctors. Thus, patients failing combined topical and systemic 5-ASA and steroid therapy should be reinvestigated for other causes of therapeutic failure, such as co-existing IBS, patient compliance, drug hypersensitivity, infections (e.g., *C. difficile*, CMV/bacterial superinfection) and proximal disease extension. In patients with refractory disease, escalation of treatment to thiopurines and anti-TNF can be recommended [84]. UP patients with severe initial disease should be considered for more aggressive treatment from the beginning, as they are more likely to develop disease extension during the course of their disease.

The efficacy of alternative treatment options, including Chinese herbal preparation, Xilai San is conflictive and warrant further investigations. The use of other experimental therapies (e.g., elective appendectomy or infliximab and cyclosporine enemas, arsenic and tacrolimus suppositories) should also be restricted for clinical trials and exceptional

cases in expert centres. Nevertheless, before these potentially promising approaches become the routine part of the therapeutic armamentarium, better understanding of their mechanism of action and solid evidence for their efficacy are needed. Proctocolectomy with IPAA may be considered as ultimate treatment in refractory proctitis cases.

Long-term maintenance treatment, especially with topical (or oral) 5-ASA therapy is recommended. However, long-term adherence is suboptimal. In mild proctitis cases with long-term clinical remission, intermittent therapy or no maintenance therapy is an option. In initially moderate-to-severe cases, combined oral (1 – 1.5 g/day) and topical 5-ASA (e.g., 1 g 5-ASA suppositories three times per week) should be the treatment of choice even for maintenance. The risk of CRC is not increased in UP; therefore, routine endoscopic surveillance is not recommended.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.

1. Ordas I, Eckmann L, Talamini M, et al. Ulcerative colitis. *Lancet* 2012;380:1606-19
- **A current review on ulcerative colitis, with special regard to pathophysiology.**
2. Satsangi J, Silverberg MS, Vermeire S, et al. The montreal classification of inflammatory bowel disease. controversies, consensus, and implications. *Gut* 2006;55:749-53
3. D'Haens G, Geboes K, Peeters M, et al. Patchy cecal inflammation associated with distal ulcerative colitis. a prospective endoscopic study. *Am J Gastroenterol* 1997;92:1275-9
4. Lakatos PL. Recent trends in the epidemiology of inflammatory bowel diseases. up or down? *World J Gastroenterol* 2006;12:6102-8
5. Lakatos L, Kiss LS, David G, et al. Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary. 2002-2006. *Inflamm Bowel Dis* 2011;17(2558):65
6. Henriksen M, Jahnsen J, Lygren I, et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). *Inflamm Bowel Dis* 2006;12:543-50
7. Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis. a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). *Am J Gastroenterol* 2000;95:469-73
8. Kim B, Park SJ, Hong SP, et al. Proximal disease extension and related predicting factors in ulcerative proctitis. *Scand J Gastroenterol* 2014;49:177-83
9. Langholz E, Munkholm P, Davidsen M, et al. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. *Scand J Gastroenterol* 1996;31:260-6
10. Ayres RC, Gillen CD, Walmsley RS, et al. Progression of ulcerative proctosigmoiditis: incidence and factors influencing progression. *Eur J Gastroenterol Hepatol* 1996;8:555-8
11. Pica R, Paoluzi OA, Iacopini F, et al. Oral mesalazine (5-ASA) treatment may protect against proximal extension of mucosal inflammation in ulcerative proctitis. *Inflamm Bowel Dis* 2004;10:731-6
12. Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent ulcerative colitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:513-19
13. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462-76
14. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699-710
15. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:85-95.quiz e14-5
16. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:96-109.e1
17. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for

- induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011;60:780-7
18. van Bodegraven AA, Boer RO, Lourens J, et al. Distribution of mesalazine enemas in active and quiescent ulcerative colitis. *Aliment Pharmacol Ther* 1996;10:327-32
 19. Brunner M, Vogelsang H, Greinwald R, et al. Colonic spread and serum pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis. *Aliment Pharmacol Ther* 2005;22:463-70
 20. Cortot A, Maetz D, Degoutte E, et al. Mesalamine foam enema versus mesalamine liquid enema in active left-sided ulcerative colitis. *Am J Gastroenterol* 2008;103:3106-14
 21. Desreumaux P, Ghosh S. Review article. mode of action and delivery of 5-aminosalicylic acid-new evidence. *Aliment Pharmacol Ther* 2006;24(Suppl 1):2-9
 22. Marshall JK, Irvine EJ. Rectal aminosalicilate therapy for distal ulcerative colitis: a meta-analysis. *Aliment Pharmacol Ther* 1995;9:293-300
 23. Lamet M. A multicenter, randomized study to evaluate the efficacy and safety of mesalamine suppositories 1 g at bedtime and 500 mg twice daily in patients with active mild-to-moderate ulcerative proctitis. *Dig Dis Sci* 2011;56:513-22
 24. Andus T, Kocjan A, Muser M, et al. Clinical trial: a novel high-dose 1 g mesalamine suppository (Salofalk) once daily is as efficacious as a 500-mg suppository thrice daily in active ulcerative proctitis. *Inflamm Bowel Dis* 2010;16:1947-56
 25. Cohen RD, Woseth DM, Thisted RA, et al. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;95:1263-76
 - **A meta-analysis of treatment options for ulcerative proctitis.**
 26. Watanabe M, Nishino H, Sameshima Y, et al. Randomised clinical trial: evaluation of the efficacy of mesalazine (mesalamine) suppositories in patients with ulcerative colitis and active rectal inflammation – a placebo-controlled study. *Aliment Pharmacol Ther* 2013;38:264-73
 27. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. *Gut* 1997;40:775-81
 28. Gionchetti P, Rizzello F, Venturi A, et al. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. *Dis Colon Rectum* 1998;41:93-7
 29. Hebden JM, Blackshaw PE, Perkins AC, et al. Limited exposure of the healthy distal colon to orally-dosed formulation is further exaggerated in active left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2000;14:155-61
 30. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012;10:CD000543
 - **A Cochrane review on oral mesalazine in the induction treatment of active ulcerative colitis.**
 31. Dignass AU, Bokemeyer B, Adamek H, et al. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;7:762-9
 32. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: the ASCEND I trial. *Can J Gastroenterol* 2007;21:827-34
 33. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005;100:2478-85
 34. Sandborn WJ, Regula J, Feagan BG, et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. *Gastroenterology* 2009;137:1934-43.e1-3
 35. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997;92:1867-71
 36. Lemann M, Galian A, Rutgeerts P, et al. Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1995;9:557-62
 37. Campieri M, Cottone M, Miglio F, et al. Beclomethasone dipropionate enemas versus prednisolone sodium phosphate enemas in the treatment of distal ulcerative colitis. *Aliment Pharmacol Ther* 1998;12:361-6
 38. Hanauer SB, Robinson M, Pruitt R, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. *Gastroenterology* 1998;115:525-32
 39. Biancone L, Gionchetti P, Blanco Gdel V, et al. Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: a multicenter, randomized, double-blind study. *Dig Liver Dis* 2007;39:329-37
 40. Mulder CJ, Fockens P, Meijer JW, et al. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. *Eur J Gastroenterol Hepatol* 1996;8:549-53
 41. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955;2:1041-8
 42. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. *Br Med J* 1954;2:375-8
 43. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012;6:991-1030
 - **ECCO consensus guideline on the management of ulcerative colitis.**
 44. Jarnerot G, Rolny P, Sandberg-Gertzen H. Intensive intravenous treatment of ulcerative colitis. *Gastroenterology* 1985;89:1005-13
 45. Seibold F, Fournier N, Beglinger C, et al. Topical therapy is underused in patients with ulcerative colitis. *J Crohns Colitis* 2014;8:56-63
 46. Cervený P, Bortlík M, Kubena A, et al. Nonadherence in inflammatory bowel disease: results of factor analysis. *Inflamm Bowel Dis* 2007;13:1244-9

47. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841-5
48. Park SK, Yang SK, Ye BD, et al. The long-term efficacy of azathioprine in steroid-dependent ulcerative colitis. *Scand J Gastroenterol* 2013;48:1386-93
49. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;146:392-400.e3
50. Bouguen G, Roblin X, Bourreille A, et al. Infliximab for refractory ulcerative proctitis. *Aliment Pharmacol Ther* 2010;31:1178-85
51. Sandborn WJ, Tremaine WJ, Schroeder KW, et al. A placebo-controlled trial of cyclosporine enemas for mildly to moderately active left-sided ulcerative colitis. *Gastroenterology* 1994;106:1429-35
52. Lawrance IC, Copeland TS. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. *Aliment Pharmacol Ther* 2008;28:1214-20
53. van Dieren JM, van Bodegraven AA, Kuipers EJ, et al. Local application of tacrolimus in distal colitis: feasible and safe. *Inflamm Bowel Dis* 2009;15:193-8
54. Schmidt KJ, Herrlinger KR, Emmrich J, et al. Short-term efficacy of tacrolimus in steroid-refractory ulcerative colitis-experience in 130 patients. *Aliment Pharmacol Ther* 2013;37:129-36
55. Molnar T, Farkas K, Nagy F, et al. Topically administered infliximab can work in ulcerative proctitis despite the ineffectiveness of intravenous induction therapy. *Am J Gastroenterol* 2009;104:1857-8
56. Makiyama K, Takeshima F, Hamamoto T. Efficacy of rebamipide enemas in active distal ulcerative colitis and proctitis: a prospective study report. *Dig Dis Sci* 2005;50:2323-9
57. Bolin TD, Wong S, Crouch R, et al. Appendicectomy as a therapy for ulcerative proctitis. *Am J Gastroenterol* 2009;104:2476-82
58. Bageacu S, Coatmeur O, Lemaitre JP, et al. Appendicectomy as a potential therapy for refractory ulcerative proctitis. *Aliment Pharmacol Ther* 2011;34:257-8
59. Sinha A, Nightingale J, West KP, et al. Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* 2003;349:350-7
60. Kono T, Nomura M, Kasai S, et al. Effect of ecabet sodium enema on mildly to moderately active ulcerative proctosigmoiditis: an open-label study. *Am J Gastroenterol* 2001;96:793-7
61. Arlander E, Ost A, Stahlberg D, et al. Ropivacaine gel in active distal ulcerative colitis and proctitis – a pharmacokinetic and exploratory clinical study. *Aliment Pharmacol Ther* 1996;10:73-81
62. Joos S, Rosemann T, Szecsenyi J, et al. Use of complementary and alternative medicine in Germany—a survey of patients with inflammatory bowel disease. *BMC Complement Altern Med* 2006;6:19
63. Ng SC, Lam YT, Tsoi KK, et al. Systematic review: the efficacy of herbal therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:854-63
- **Systematic review with a spotlight on complementary and alternative medicine.**
64. Holt PR, Katz S, Kirshoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. *Dig Dis Sci* 2005;50:2191-3
65. Brunel M, Penna C, Tiret E, et al. Restorative proctocolectomy for distal ulcerative colitis. *Gut* 1999;45:542-5
66. Shen B, Lashner BA, Bennett AE, et al. Treatment of rectal cuff inflammation (cuffitis) in patients with ulcerative colitis following restorative proctocolectomy and ileal pouch-anal anastomosis. *Am J Gastroenterol* 2004;99:1527-31
67. Wu B, Lian L, Li Y, et al. Clinical course of cuffitis in ulcerative colitis patients with restorative proctocolectomy and ileal pouch-anal anastomoses. *Inflamm Bowel Dis* 2013;19:404-10
68. Richter JM, Kushkuley S, Barrett JA, et al. Treatment of new-onset ulcerative colitis and ulcerative proctitis. a retrospective study. *Aliment Pharmacol Ther* 2012;36:248-56
69. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012;10:CD000544
- **A Cochrane review on oral mesalazine in the maintenance treatment of ulcerative colitis.**
70. Hanauer S, Good LI, Goodman MW, et al. Long-term use of mesalamine (Rowasa) suppositories in remission maintenance of ulcerative proctitis. *Am J Gastroenterol* 2000;95:1749-54
71. d'Albasio G, Paoluzi P, Campieri M, et al. Maintenance treatment of ulcerative proctitis with mesalazine suppositories: a double-blind placebo-controlled trial. The Italian IBD Study Group. *Am J Gastroenterol* 1998;93:799-803
72. Marteau P, Crand J, Foucault M, et al. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. *Gut* 1998;42:195-9
73. d'Albasio G, Trallori G, Ghetti A, et al. Intermittent therapy with high-dose 5-aminosalicylic acid enemas for maintaining remission in ulcerative proctosigmoiditis. *Dis Colon Rectum* 1990;33:394-7
74. Lennard-Jones JE, Misiewicz JJ, Connell AM, et al. Prednisone as Maintenance Treatment for Ulcerative Colitis in Remission. *Lancet* 1965;1:188-9
75. Kirk AP, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. *Br Med J (Clin Res Ed)* 1982;284:1291-2
76. Hawthorne AB, Logan RF, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992;305:20-2
77. Ardizzone S, Maconi G, Russo A, et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006;55:47-53
78. Kruis W, Schutz E, Fric P, et al. Double-blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 1997;11:853-8
79. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526-35

80. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012;10:639-45
81. Lopez A, Peyrin-Biroulet L. 5-Aminosalicylic acid and chemoprevention: does it work? *Dig Dis* 2013;31:248-53
82. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J Crohns Colitis* 2013;7:1-33
83. Marshall JK, Irvine EJ. Putting rectal 5-aminosalicylic acid in its place: the role in distal ulcerative colitis. *Am J Gastroenterol* 2000;95:1628-36
84. Ng SC, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. *Inflamm Bowel Dis* 2009;15:935-50
- **An important review article on the therapeutic approaches in ulcerative colitis.**

Affiliation

Krisztina B Gecse¹ MD PhD &

Peter L Lakatos^{†2} MD PhD

[†]Author for correspondence

¹Assistant Lecturer,

Semmelweis University, 1st Department of

Medicine, Korányi Sándor utca 2a,

H1083 Budapest, Hungary.

Tel: +36 20 9117727;

Fax: +36 1 3130250;

E-mail: lakatos.peter_laszlo@med.semmelweis-univ.hu

²Associate Professor,

Semmelweis University, 1st Department of

Medicine, Korányi Sándor utca 2a,

H1083 Budapest, Hungary