**TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF ULCERATIVE COLITIS**
*TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN ÜLSERATİF KOLİT İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ*

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# Should maintenance therapy be performed in ulcerative proctitis? How long should it be continued?

*Ülseratif proktitte idame tedavisi yapılmalı mı? Ne kadar süre yapılmalı?*

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## INTRODUCTION

In one-third of all ulcerative colitis (UC) cases, the rectum or distal colon was involved. Ulcerative proctitis is a disease limited to the rectum. Distinct from the other types of UC, there are no acute complications like toxic megacolon and colorectal cancer risk. The course of ulcerative proctitis is variable; it may be associated with remission or relapse, or it may show a refractory course. 5-Aminosalicylic acid (5-ASA) suppository, 5-ASA enema and oral 5-ASA preparations are the medications that may be used in the maintenance treatment of ulcerative proctitis; combination (oral + rectal) treatment may also be administered. There is no use of oral or topical steroids in the maintenance treatment of ulcerative proctitis. There is no clear consensus regarding the maintenance treatment of ulcerative proctitis or its duration. The maintenance treatment may be administered to prevent possible relapse, proximal spread or development of colorectal cancer. This study was performed to offer suggestions by reviewing all the literature based on these three parameters.

## MATERIALS AND METHODS

A search in Medline was performed with the following key words by using systematic literature scan: “proctocolitis and maintenance treatment”, “ulcerative proctitis and maintenance treatment”, “ulcerative proctitis and maintenance treatment and mesalazine”, "colitis, ulcerative" [Mesh] and maintenance treatment”, “ulcerative proctitis and proximal extension”, “ulcerative proctitis and prognosis”, and “ulcerative proctitis and colon cancer”. All of the studies performed in an adult group were included into the assessment. Additionally, other studies were attained by scanning literature references. Should maintenance therapy be performed in ulcerative proctitis? Aiming to find a response to the question, “How long should it be continued?”, 10 studies were attained in consequence of scanning 729 literatures. All of the studies analyzed were retrospective. Relapse rate, proximal spread of the disease and colon cancer were used as analysis and evaluation criteria.

## RESULTS

Only a small number of ulcerative proctitis cases can discontinue the treatment, and 47%-86% of them relapse within one year (1). Female gender and younger age are risk factors for relapse (2). Long-term epidemiological studies have shown that ulcerative proctitis could later develop more proximal colitis or pancolitis. It has been determined that 22% of ulcerative proctitis cases had proximal spread within 1-2 years despite medical treatment (3). In two long-term epidemiological studies (10 years), it was found that 32% and 41% of ulcerative proctitis cases had proximal spread, respectively (4,5). In the study performed by the IBSEN group, proximal spread was seen in 28% of the cases and progression to extensive colitis in 10% of the cases in five years (2). It has been shown that proximal spread of the disease could be prevented with oral mesalazine treatment (6).

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In a long-term retrospective screening, proximal spread and spread as far as the splenic flexure in 273 ulcerative proctitis cases were found to be 20% and 4% in the 5th year and 54% and 10% in 10th year, respectively. Proximal spread risk was found to be higher in individuals not smoking, having more than three relapses in a year, and requiring systemic steroid and azathioprine (refractory disease) (7). When all of the literature was searched, it was seen that colorectal cancer risk did not increase in ulcerative proctitis cases (8-10, ECCO statement 9B, 9L) (Table 1).

A study directly answering the question, "How long should maintenance treatment be continued?", could not be found, but in long-term follow-up studies, it was shown that the relapse rate in patients with distal colitis was lower and occurred in advanced stages compared to those with pancolitis and left-sided colitis (11). Randomized-controlled studies were performed regarding maintenance treatment of ulcerative proctitis.

### In Randomized-Controlled Studies Regarding Mesalamine Suppository and Placebo

Mesalamine suppository 800 mg (12 months) and placebo (12 months) were compared, and mesalamine treatment was found to be superior in the maintenance of remission (12). Mesalamine suppository 1 g (3 days/week for 6 months, 12 months, 24 months) and placebo (3 days/week for 6 months, 12 months, 24 months) were compared, and mesalamine treatment was found to be superior in the maintenance of remission (13). Mesalamine suppository 500 mg (12 months, 24 months) and placebo (12 months, 24 months) were compared, and mesalamine treatment was found to be superior in the maintenance of remission (1). Mesalamine suppository 500 mg, 1 g (12 months) and placebo (12 months) were compared, and mesalamine 1 g treatment was found to be superior to mesalamine 500 mg, and mesalamine treatment (500 mg, 1 g) was found to be superior to placebo (14).

**Table 1.** Colorectal cancer development together with ulcerative colitis involvement (Gastroenterology 2010; 138: 746-74)

| Colonic involvement | Colorectal Ca RR (95% CI) |
|---|---|
| Pancolitis | 14.8 (11.4-18.9) |
| Left-sided colitis | 2.8 (1.6-4.4) |
| Proctitis | 1.7 (0.8-3.2) |

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### In Randomized-Controlled Studies Regarding Budesonide Enema and Placebo

Budesonide enema (2 days/week for 6 months) and placebo (6 months) were compared, and budesonide was not found to be superior to placebo in the maintenance of remission (15).

### In Randomized-Controlled Studies Regarding Mesalamine Enema and Oral 5-ASA Preparations

When 5-ASA 4 g enema treatment (daily in the first week of the month) and daily 2 g sulfasalazine treatment were compared, no significant difference was found regarding two-year relapse rates (16). When mesalamine 4 g enema treatment (once in 3 days) and mesalamine 1.5 g tablet (daily) treatments were compared, two-year remission rates in the enema arm were found to be statistically significantly higher than in the tablet arm (74%, 32%, respectively; $p<0.001$) (17).

### In Randomized-Controlled Studies Regarding Combined Treatment

When 5-ASA tablet (1.6 g/day) + 5-ASA enema 4 g (2 days/week) treatment was compared with 5-ASA tablet (1.6 g/day) + placebo (2 days/week) treatment, relapse rates in the combined treatment arm were found to be statistically significantly lower than in the oral treatment arm (39%, 69%, respectively; $p<0.036$) (18).

Refractory proctitis is a different entity, and its maintenance treatment shows variation compared to classical ulcerative proctitis. The causes of refractory proctitis can be drug non-compliance, inadequate active drug levels, erroneous drug administration, proximal constipation, infection, and comorbidity of irritable bowel syndrome, Crohn's disease, mucosal prolapse, and very rarely, cancer. Proximal constipation should be treated. If inflammation persists in sigmoidoscopy despite topical mesalazine and oral steroid, plain abdominal radiograph is recommended. In case of observation of fecal burden in the descending colon, it is suitable to administer laxative. If the symptoms do not regress in two to four weeks, then it should be treated as a serious disease. Treatment with cyclosporine, tacrolimus or biological agents may be tried. In cases unresponsive to treatment, ileoanal pouch and total colectomy are recommended (ECCO 5.2.7). If remission is obtained with azathioprine in a case with refractory proctitis, azathioprine is recommended in the maintenance treatment (19).

## CONCLUSION

Maintenance treatment in ulcerative proctitis cases may prevent possible relapse and proximal spread. Maintenance treatment is not recommended to prevent colorectal cancer, since it has been observed in many studies that colorectal cancer did not develop in ulcerative proctitis cases (8-10, ECCO statement 9B, 9L). Randomized-controlled studies have been performed regarding maintenance treatment in ulcerative proctitis cases. All of the randomized-controlled studies were analyzed, and "Number-Needed to Treat" (NNT) values of each study calculated separately are shown in Table 2.

**Table 2.** The results of analyses of randomized-controlled studies regarding maintenance treatment

| |
|---|
| Mesalamine 800 mg supp 12 mo/placebo: NNT: 1.4 |
| Mesalamine 1 g supp (3/7) 12 mo/placebo: NNT: 7 |
| Mesalamine 1 g supp 6 mo/placebo: NNT: 4 |
| Mesalamine 500 mg supp 12 mo/placebo: NNT: 5.8 |
| Mesalamine 500 mg supp 24 mo/placebo: NNT: 2.86 |
| Mesalamine 1 g supp 12 mo/placebo: NNT: 2.5 |
| Budesonide enema 2/7 (6 mo)/placebo: NNT: 7 |
| Mesalamine enema (7 days/mo) 12 mo/oral sulfasalazine: NNT: 1.25 |

NNT: Number-needed to treat. Mo: Months.

In conclusion, in maintenance treatment, mesalamine suppository treatments were found to be superior to placebo, mesalamine enema treatment was found to be superior to mesalamine oral treatment, and combined treatment (oral + rectal) was found to be superior to oral treatment (1,12-14,17,18). Budesonide enema was not found to be effective in maintenance treatment (15).

***Recommendation:***

*Maintenance treatment in ulcerative proctitis may be administered to prevent relapse risk and possible proximal spread of the disease.* ***(EL 2b, RG B)***

*In maintenance treatment, 5-ASA suppository/enema (3 days/week) is recommended. If there is frequent relapse (>2/year), the dose may be given every day or combination treatments (oral+rectal) are recommended.* ***(EL5, RG D)***

*Azathioprine/6-Mercaptopurine (AZA/6-MP) is recommended in the maintenance treatment of refractory proctitis.* ***(EL5, RG D)***

*The treatment can be stopped, if patients are still in remission after 2 years of maintenance therapy.* ***(EL5, RG D)***

*Studies determining how long maintenance treatment should be performed are required.* ***(EL5, RG D)***

## REFERENCES


1. 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.
2. Henriksen M, Jahnsen J, Lygren I, et al.; IBSEN Study Group. 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.
3. Moum B, Ekbom A, Vatn MH, et al. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. Am J Gastroenterol 1999; 94: 1564-9.
4. 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.
5. Solberg IC, Lygren I, Jahnsen J, et al.; IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol 2009; 44: 431-40.
6. 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.
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. Herszenyi L, Miheller P, Tulassay Z. Carcinogenesis in inflammatory bowel disease. Dig Dis 2007; 25: 267-9.
9. Kvist N, Jacobsen O, Kvist HK, et al. Malignancy in ulcerative colitis. Scand J Gastroenterol 1989; 24: 497-506.
10. Farraye FA, Odze RD, Eaden J, et al. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010; 138: 746-74.
11. Bresci G, Parisi G, Bertoni M, et al. Long-term maintenance treatment in ulcerative colitis: a 10-year follow-up. Dig Liver Dis 2002; 34: 419-23.

12. D'Arienzo A, Panarese A, D'Armiento FP, et al. 5-Aminosalicylic acid suppositories in the maintenance of remission in idiopathic proctitis or proctosigmoiditis: a double-blind placebo-controlled clinical trial. Am J Gastroenterol 1990; 85: 1079-82.
13. 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.
14. 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.
15. Lindgren S, Löfberg R, Bergholm L, et al. Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis. Scand J Gastroenterol 2002; 37: 705-10.
16. 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.
17. Mantzaris GJ, Hatzis A, Petraki K, et al. Intermittent therapy with high-dose 5-aminosalicylic acid enemas maintains remission in ulcerative proctitis and proctosigmoiditis. Dis Colon Rectum 1994; 37: 58-62.
18. D'Albasio G, Pacini F, Camarri E, et al. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. Am J Gastroenterol 1997; 92: 1143-7.
19. Ng SC, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. Inflamm Bowel Dis 2009; 15: 935-50.