

WJGP 5th Anniversary Special Issues (2): Ulcerative colitis**“Mucosal healing” in ulcerative colitis: Between clinical evidence and market suggestion**

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Core tip: In recent years, the concept that the management of ulcerative colitis patients should aim to heal the mucosa rather than resolve symptoms has been decisively proposed. Herein, we review the current evidence supporting this statement and analyze the possible practical implications in the current management of ulcerative colitis patients.

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Abstract

In recent decades, the prominent role of endoscopy in the management of ulcerative colitis (UC) has been translated into the concept of mucosal healing (MH) as a fundamental therapeutic end-point. This is partially the consequence of growing evidence of a positive prognostic role of MH on the disease course and partially due to market cues indicating a higher rate of MH in patients treated by novel potent biologic agents. The aim of the present review is to clarify the current knowledge of MH in UC, analyzing the definition, the putative prognostic role and the association of MH with the current drugs used to treat UC patients. Because solid data about the management of UC patients based solely on the healing of the mucosa are not yet available, a tailored approach for individual patients that considers the natural history of UC and the presence of prognostic indicators of aggressive disease is desirable. Consequently, unnecessary examinations and treatment would be avoided and restricted to UC patients who require the maximum amount of effort to affect the disease course in the short and long term.

INTRODUCTION

A crucial topic that physicians have long faced in the management of ulcerative colitis (UC) patients is the identification of a reference parameter for the assessment of disease activity. Indeed, UC is a chronic inflammatory disease of the colon, characterized by limitation of the inflammation to the mucosa and the proximal extension of the disease starting from the rectum^[1]. Indeed, the term “UC” comprises a heterogeneous condition with differing involvement of the colon in terms of its extension and the grade of inflammation, which in turn can lead to possible alterations of laboratory parameters and symptom occurrence and severity. The clinical, biochemical and mucosal alterations do not always directly correlate, and questions have been raised about which parameter should be used as the “gold standard” for disease activity assessment.

For the capacity to directly evaluate the colon, which is the target organ of the disease, endoscopy has been indicated as the more accurate tool to assess the activity of the disease, further supported by the possible misleading role of symptoms in the evaluation of UC patients^[2,3]. Unfortunately, colonoscopy is an invasive, costly and time-consuming procedure, and the routine repetition of the examination is not feasible. Different objective surrogate parameters have been described to aid physicians in the correct evaluation of the activity state of patients with inflammatory bowel disease (IBD), including serological (*i.e.*, C-reactive protein) and fecal (*i.e.*, calprotectin, lactoferrin) markers^[4], as well as clinical scores^[5].

During the last decade, the addition to the IBD therapeutic arsenal of anti-TNF- α biologic drugs, which were formerly used in other chronic inflammatory conditions, has launched a “Copernican revolution” in the clinical approach to both Crohn’s disease (CD) patients and UC patients. In fact, together with a rapid and consistent improvement of symptoms and laboratory parameters, such potent anti-inflammatory compounds have resulted in rapid and dramatic improvements of the intestinal mucosal lesions characteristic of IBD, as documented by endoscopic evaluation before and after the induction therapy^[6]. Since this time, the relevance of the endoscopic activity of disease has been definitively stated, and “mucosal healing” (MH) has been proposed with increasing strength as a fundamental therapeutic goal of IBD treatment, claiming its prognostic relevance in the natural history of the disease^[3]. Since the first studies that described the efficacy of Infliximab in CD patients^[7,8], some 15 years have passed, and the therapeutic options for IBD patients have consistently expanded. At present, two biologic anti-TNF agents are currently approved in Europe for utilization in both CD and UC (Infliximab and Adalimumab), and some biologic agents have already shown efficacy in randomized clinical trials and are indicated for market release^[9]. The emphasis on the efficacy of such novel drugs for the amelioration of mucosal inflammation has contributed to making the concept of MH a paramount therapeutic goal, and we are passing from a symptom-targeted to a mucosa-targeted approach in the management of IBD patients^[10]. Several observations have contributed to encourage this shift in IBD management, outlining the relation between mucosal healing and the favorable long-term outcome of the disease in terms of reductions in flares, hospitalizations, the need for surgery and cancer incidence^[11].

Although the MH concept has recently been particularly emphasized in CD, the importance of endoscopic remission in UC has been known for a long time^[12]. In fact, the achievement of MH in UC appears of particular relevance for the localization of the disease (mucosal and limited to the colon), which renders the endoscopic examination relatively easier compared with CD, in which the inflammation is transmural and can potentially involve areas of the intestine not accessible to endoscopic inspection. Considering that more than half of

UC patients present inflammation limited to the left side of the colon^[13], the possibility that the involved areas can be easily scoped to evaluate MH in such patients is particularly tempting.

Nonetheless, specific treat-to-target studies addressing the effective role on the natural progression of the disease of a treatment strategy focused electively on the achievement of MH are still lacking. The relevance of MH to the management of UC, although intriguing and rational, remains to be firmly established. The possibility that the importance of MH would tend to be overrated due to the influence of sponsored trials underlining the association between MH and biologic drugs must be considered. Moreover, data coming from randomized clinical trials (RCTs) are usually not completely applicable to the “real-life” IBD population. In fact, a recent retrospective analysis of consecutive mild-moderate IBD patients at a United States tertiary referral center found that only 31.1% of patients would fulfill the inclusion criteria of the major RCTs of biologic agents and that the outcomes of patients fulfilling the criteria are significantly more favorable compared with those not meeting the criteria^[14].

Besides scientific and commercial suggestions, a careful revision of the actual evidence in support of MH is essential. The risk of a blind and excessively enthusiastic adherence to the MH suggestion is concrete, and physicians need to be aware of the over-prescription of unnecessary endoscopic examinations and/or the over-treatment of patients. In an era of resource optimization, this would risk minimizing the same advantages that the MH strategy is claiming, *i.e.*, the reduction of disease costs by reducing complications and hospitalizations. Extensive systematic reviews of MH are already available in the literature (*i.e.*, Neurath *et al.*^[11]), and such a review is beyond the aim of the present work. Here, we intend to perform a synthetic and careful revision of the state-of-the art research on MH. To this end, we critically reviewed the definition of MH, the quality of the actual evidence of its prognostic relevance, and the capacity of the therapies currently used for UC to achieve MH, with the final goal of clarifying the potential correct application of the concepts of MH to the current practical management of patients affected by UC.

MH: DEFINITION

Although a standardized definition of MH has not been established, a practical currently accepted definition is “the complete resolution of the visible alterations or lesions, irrespective of their severity and/or type at baseline colonoscopy”^[11]. Nonetheless, at present, an easy to use, validated and clinically relevant endoscopic score for UC activity evaluation is lacking, reflecting the complexity in measuring disease activity in UC^[15]. In fact, although a great number of scoring systems have been developed (Baron score, Mayo score, Sutherland, Powell-Tuck and Rachmilewitz indices, among others)^[16-24], none of them have been prospectively validated. The main problems

regarding the majority of the indices include the overlap of mucosal features (such as vascularity, granularity, erythema, friability, bleeding, and ulceration), leading to inter-observer variation in endoscopic evaluation, and the lack of clear and standardized thresholds for endoscopic remission or improvement. The Mayo Clinic endoscopy subscore has been the most commonly used in recent clinical trials, defining MH as a score of ≤ 1 (normal mucosa or loss of vascular pattern, but no mucosal friability), when the endoscopy subscore was 2 or 3 at baseline. The problem of a standardized definition of MH is not theoretical but implies concrete and practical consequences. In fact, in recent clinical trials, heterogeneous definitions may have contributed to the higher rate of patients with MH when compared with that of patients achieving clinical remission^[25], although alternative explanations are possible (*e.g.*, the simultaneous presence of irritable bowel syndrome, dysmotility). Moreover, a recent RCT testing the use of mesalamine in UC patients showed consistently different results after a revision of the endoscopic examination findings by a blinded central reader^[26].

In further support of the aforementioned difficult evaluation of UC endoscopic activity, two novel scores have been very recently developed and prospectively validated, the Ulcerative Colitis Endoscopic Index of Severity and the Ulcerative Colitis Colonoscopic Index of Severity^[27,28]. Data about the applicability of such new scores in clinical trials and in clinical practice are awaited and will hopefully aid the move toward a standardized definition of MH.

Recently, data indicating a prognostically relevant role for histologic activity in the mucosa of UC patients, in addition to the macroscopic activity, have opened the door to the concept of “histological MH”, with the complete absence of clinical, laboratory, endoscopic and histological features of active inflammation^[29]. Indeed, the term “mucosal healing” was initially proposed only for the disappearance of the inflammatory infiltrate in the histological examination^[30]. At present, although some scoring systems for histologic activity have been described, none have been properly validated or commonly used, and therefore, the definition of histological MH remains without consensus.

MH: EVIDENCE FOR PROGNOSTIC RELEVANCE

The increasing relevance of the MH achievement in UC has been demonstrated by a growing body of data showing the different courses of the disease in patients with and without MH, with a reduction of complications such as flares as well as reductions in hospitalization, colectomy and cancer incidence in patients with MH.

As early as 1966, Wright *et al.*^[31] reported a higher relapse rate in patients who did not achieve MH after oral and rectal steroids when compared with patients who did achieve MH (40% *vs* 18%). In the ACT1 and ACT2

trials, patients treated with infliximab who exhibited MH at week 8 showed a higher rate of clinical remission at week 30 than patients without MH (48.3% *vs* 9.5%)^[32]. Yamamoto *et al.*^[33] reported that UC patients who achieved clinical remission and MH after leukocytapheresis had a higher rate of sustained clinical response when compared with patients with only a clinical response (88% *vs* 41%). Ardizzone *et al.*^[34] showed that the lack of mucosal healing at 3 mo after the first corticosteroid treatment was the only factor associated with negative outcomes at 5 years (use of immunosuppressants, hospitalization and colectomy).

An observational study of the IBSEN cohort showed that in 513 UC patients, the colectomy rate was lower in patients with MH [defined by a simple endoscopic score of 0-1 (0, normal; 1, light erythema or granularity)] at a 5-year follow-up (2% *vs* 8%, $P < 0.05$)^[35]. Similar results were shown by Soldberg *et al.*^[36], who reported a decrease in the colectomy rate in UC patients with MH at 1 year after diagnosis, regardless of the therapy used to achieve it, and in a post-hoc analysis of the ACT1/ACT2 trials conducted by Colombel *et al.*^[37], in which a Mayo Clinic endoscopy subscore of 0-1 in Infliximab-treated patients was related to a lower probability of colectomy than a score of 2-3 through a follow-up period of 54 wk. Interestingly, in the latter article by Colombel *et al.*^[37], MH in the placebo group did not show the same positive prognostic value as it did in the Infliximab-treated group, questioning the prognostic value of MH “*per se*” and suggesting that the drugs used to achieve the MH may play a specific role in the long-term outcome.

The increased risk of colorectal cancer incidence in UC patients is still a matter of debate^[38]. Nonetheless, the inflammatory burden appears to be an important determinant, and consequently, MH is likely to reduce the risk. An Italian cohort study indicated a lower CRC risk at 17 years of follow-up in azathioprine (AZA)-treated UC patients with MH^[39].

Recently, appealing data have indicated a possible prognostic role for histologic remission in terms of reductions in flares, surgery/hospitalization and CRC incidence, suggesting histologic remission as the ultimate therapeutic goal in UC management^[29]. In fact, Bitton *et al.*^[40] have reported basal plasmacytosis at rectal biopsy as an independent predictor of early relapse in UC patients, and Bessisow *et al.*^[41] have described a higher rate of flares in patients with macroscopically healed mucosa but histologic activity when compared with patients with both the macro- and microscopic absence of disease. Nonetheless, correlations with macroscopic and microscopic activity are not always straightforward^[42], and routine biopsies are not suggested by the current guidelines. At present, more evidence is needed before considering histological MH as a possible goal of treatment in UC patients.

MH: CURRENT THERAPIES

Biologic agents

As mentioned, the MH concept has been clearly defined

Table 1 Randomized clinical trial of biologic agent in ulcerative colitis and the relative mucosal healing rates

Ref.	Patients (n)	Treatment protocol duration	Evaluation time from baseline	MH rate
Rutgeerts <i>et al</i> ^[32]	728	IFX 5 or 10 mg/kg every 8 wk	Week 8	60.7% IFX
		Placebo		32.3% placebo
		30 wk (ACT2)	Week 30	50.6% IFX
Panaccione <i>et al</i> ^[50]	231	AZA 2.5 mg/kg	Week 16	27.4% placebo
		IFX 5 mg/kg		46.0% IFX
		IFX 5 mg/kg + AZA 2.5 mg/kg		18.2% placebo
Sandborn <i>et al</i> ^[25]	494	ADA 160/80 and then 40 mg eow	Week 8	37% AZA
		Placebo		55% IFX
		54 wk (ACT1)	Week 54	63% AZA + IFX
Reinisch <i>et al</i> ^[43]	390	ADA 160/80 mg or 80/40 mg at weeks 0 and 2 followed by 40 mg at weeks 4 and 6	Week 8	41.1% ADA
		Placebo		31.7% placebo
		52 wk	Week 52	25.0% ADA
Feagan <i>et al</i> ^[44]	225	VED 300 mg at week 0 and 2 and then every 4 or 8 wk	Week 6	15.4% placebo
		Placebo		46.9% ADA (160/80)
		52 wk	Week 52	37.7% ADA (80/40)
Sandborn <i>et al</i> ^[45,46]	774	GOL 400/200 or 200/100 mg at weeks 0 and 2 followed by 50 mg or 100 mg every 4 wk	Week 6	41.5% placebo
		Placebo		54% ADA
		54 wk	Week 54	40.7% VED
Feagan <i>et al</i> ^[44]	225	VED 300 mg at week 0 and 2 and then every 4 or 8 wk	Week 6	24.8% placebo
		Placebo		56% VED (every 4 wk)
		52 wk	Week 52	51.6% VED (every 8 wk)
Sandborn <i>et al</i> ^[45,46]	774	GOL 400/200 or 200/100 mg at weeks 0 and 2 followed by 50 mg or 100 mg every 4 wk	Week 6	19.8% placebo
		Placebo		45.1% GOL (400/200)
		54 wk	Week 54	42.3% GOL (200/100)
Sandborn <i>et al</i> ^[45,46]	774	GOL 400/200 or 200/100 mg at weeks 0 and 2 followed by 50 mg or 100 mg every 4 wk	Week 6	28.7% placebo
		Placebo		42.4% GOL100 every 4 wk
		54 wk	Week 54	41.7% GOL 50 every 4 wk
Sandborn <i>et al</i> ^[45,46]	774	GOL 400/200 or 200/100 mg at weeks 0 and 2 followed by 50 mg or 100 mg every 4 wk	Week 6	26.6% placebo
		Placebo		
		54 wk	Week 54	

MH: Mucosal healing; IFX: Infliximab; ADA: Adalimumab; AZA: Azathioprine; VED: Vedolizumab; GOL: Golimumab.

only in the biologic era, and the trials of biologic drugs present a better evaluation of this aspect than previous studies. In particular, the MH definition has been standardized by the utilization of the Mayo endoscopic subscore, which identifies as MH as a score of 0 or 1. However, MH has always been considered as a secondary end-point in clinical trials, and studies still present heterogeneity in terms of inclusion criteria (and, therefore, baseline endoscopic severity), design and follow-up. Nonetheless, the MH rates in the short (induction) and long term (maintenance) are consistent and significantly superior to those of placebo in all studies (Table 1), which is even more remarkable considering the baseline severity of the UC patients included, although, in most of the studies, MH was only observed in a minority of the patients^[25,32,43-46]. Moreover, as mentioned, patients in RCTs are superselected, and the results may be not directly applicable to the “real-life” IBD population.

Azathioprine

From the first early report by Jewell *et al*^[47] of increased MH after 4 wk in UC patients treated with corticosteroids plus AZA *vs* corticosteroids plus placebo (92% *vs* 71%, $P = ns$), few studies with a limited number of patients have addressed MH rates in AZA-treated UC patients. In all of the reported studies, MH was a secondary end-

point, and the MH definition, base-line endoscopic activity, timing of the endoscopic evaluation and concomitant therapies differed; therefore, conclusive results are hard to extrapolate.

With the aforementioned limitations, Paoluzi *et al*^[48] reported 57% and 45% rates of MH in UC patients treated with AZA at 6 mo ($n = 42$ patients) and 4 years ($n = 22$ patients), respectively, and a similar 6-mo rate was reported by Ardizzone *et al*^[49] [19/36 patients treated with AZA (53%) *vs* 7/36 of patients treated by 5ASA (19%)]. Recently, a study by Panaccione *et al*^[50] (available only in abstract form) reported a 36% MH rate in patients treated with AZA in monotherapy and a 63% MH rate in patients treated with AZA plus Infliximab at 4 mo, with nearly 80 patients per group, indicating that combination therapy may increase the rate of MH.

Corticosteroids

Unlike CD, in which corticosteroids are traditionally considered ineffective for the achievement of MH^[51], corticosteroids may induce MH and a clinical response in UC. The first evidence supporting a favorable role of corticosteroids in inducing MH dates back to 1954, when True-love reported a double-blind placebo-controlled randomized multicenter trial of 120 UC patients and demonstrated higher rates of MH in the oral cortisone (100 mg/d) group

than in the placebo group (30% *vs* 10%) within 6 wk^[16].

In the last six decades, a great number of studies have reported positive effects of corticosteroid therapy on the improvement/resolution of mucosal alterations in UC, irrespective of the route of administration (oral or rectal) and the type of corticosteroids (traditional systemic steroids or agents with low systemic availability)^[52-59]. Generally, a certain discrepancy between the clinical and endoscopic responses was present in the majority of the studies evaluating MH in UC after corticosteroid treatment. A meta-analysis by Marshall *et al*^[55] examining the role of rectal corticosteroid preparations showed similar clinical (approximately 45% of cases) and endoscopic (approximately 33% of cases) remission rates for conventional corticosteroids (hydrocortisone, prednisolone, methylprednisolone and betamethasone) and topically active corticosteroids (beclomethasone, budesonide and prednisolone metasulphobenzoate). Recently, Ardizzone *et al*^[34], in a study of 157 consecutive newly diagnosed UC patients, explored the potential prognostic significance of a 3-mo clinical and endoscopic response after the first course of corticosteroid treatment. After 3 months, 60 patients (38.2%) had a complete clinical and endoscopic response, 39 (24.8%) had a clinical but not an endoscopic response, and 58 (36.9%) had no response. Interestingly, failure to achieve endoscopic remission at the end of the first course of steroids was related to a more aggressive disease behavior.

Data obtained from the use of topical steroids present a reduced variability between clinical and endoscopic responses. Indeed, in a recent meta-analysis exploring the efficacy of rectal beclomethasone dipropionate, the clinical and endoscopic rates of improvement or remission were similar (65.3%) and concordant, although in the four trials considered for the meta-analysis, a clear definition and evaluation of mucosal healing were lacking^[60].

Several problems arise in the attempt to analyze and compare the results of the above-mentioned studies. Diversity in the timing of endoscopy and in the use of endoscopic indices (*e.g.*, Sigmoidoscopic score, Rachmilewitz index, Baron score) along with the lack of a univocal MH definition, possible inter-observer variations or heterogeneity of the included patient cohorts may have generally contributed to consistent variability in the MH rates in steroid trials.

Aminosalicylates

Mesalamine was approved by the Food and Drug Administration in late 1987, and since this time, it has become the cornerstone therapy for mild-moderate UC^[61]. Mesalamine can be administered orally and/or topically, and it is present on the market in different formulations specific to both methods of administration. Many studies show the ability of mesalamine to induce MH. A recent meta-analysis of 49 studies has concluded that MH is achieved in approximately 37% and 50% of patients treated with oral and topical mesalamine, respectively^[62]. Nonetheless, the results from single studies are dramatically different,

ranging from approximately 0% to 77% for oral mesalamine^[23,63] and from approximately 10% to 93% for topical formulations^[54,64]. This variability may be attributed to the different definitions of MH, but this is unlikely to be the only reason. While MH rates do not appear to be related to the release mechanisms of oral mesalamine^[62], in accordance with previous studies reporting similar effectiveness between different formulations^[61,65,66], studies continue to present great heterogeneity in terms of total dose in grams, disease extension, months of follow up and endoscopic score at baseline. Notably, the MH rates in placebo groups are reported to be high, up to 46% in a study of oral placebo *vs* oral mesalamine at 8 wk^[63] and 26%-37% in a study of topical placebo *vs* topical mesalamine after 6 wk^[67]. Moreover, in studies with therapeutic regimens of adequate dose and duration, the MH rate appears to be higher^[68-70], and the lack of achievement of MH in patients with clinical remission has been indicated as a possible negative prognostic factor for relapse occurrence^[71].

CONCLUSION

After the emergence of novel biologic therapies for UC, the old concept of the relevance of the endoscopic activity of disease has been translated into the new concept of MH as the therapeutic goal to achieve. Although this idea has been supported by a growing body of scientific evidence indicating the favorable prognostic value of a healed mucosa in the natural history of UC, it is also suggested commercially, as a high rate of MH is claimed when utilizing the new biologic agents. Indeed, endoscopic evaluation appears to be the “gold standard” for the evaluation of disease activity in UC patients, and healing of the mucosa is likely to be an important factor for the control of the disease in the short and long term. However, specific studies showing the superiority of a management based solely on MH over the “traditional” approach are lacking. To date, most of the evidence supporting the prognostic relevance of MH comes from studies in which MH is not considered as the primary endpoint as well as from retrospective investigations. In the present study, we provocatively addressed the issue of the relevance of MH for UC patients management. A careful review of the current evidence regarding MH in UC shows that, due to the high heterogeneity of the available studies (particularly for those from the pre-biologic era), crucial points are still far from being conclusively determined, including the MH definition, the expected rate of MH with the current medication, and whether a systematic assessment of MH and an optimization of therapy based on MH alone would improve long-term disease outcome. Moreover, the prognostic value of MH “*per se*” needs to be investigated to clarify whether the current drugs may be safely reduced or interrupted after MH achievement. The latter issue may also present consistent economic implications regarding the elevated cost of long-term maintenance therapy with biologic drugs. However, in most cases, MH appears to be achiev-

able only in a minority of UC patients and most likely with the utilization of potent and potentially dangerous therapeutic regimens. In the near future, the development of novel drugs and an increase in our knowledge of the complexity of IBD are desirable, as they may increase the efficacy of our therapeutic approach to the disease.

Notably, going back to the natural history of the disease, more than one-half of UC patients have a benign disease course, while up to one-third are likely to experience frequent flares and potentially dangerous complications. In fact, the large population study by Solberg *et al.*^[36] (IBSEN cohort), which evaluated the first 10 years of the disease course in a population of 519 patients with UC, highlighted an overall good prognosis. Their study showed that at 10 years, more than half of patients were in remission or had mild disease, while 37% and 6%, respectively, reported chronic intermittent and chronic continuous symptoms. In a large Danish cohort study, approximately one-third of patients had no flares within 10 years after the first attack of UC. Moreover, the cumulative probability of having a course without relapses after 10 years in patients in remission is 40%-60%^[72]. However, the colectomy rate is estimated to vary from 8.7% to 30% in different populations^[72-74], and after the first relapse, the cumulative rates of a second course of systemic steroids are 13%, 41% and 48% at 1, 5 and 10 years, respectively^[36].

In times of resource optimization, the ideal disease management would imply an aggressive treatment and endoscopic follow-up for the achievement of MH in patients with an unfavorable disease course. Accordingly, together with a better definition of the MH concept and its specific role in the management of UC patients, further research for the characterization of clinical and/or genetic features predictive of an aggressive behavior of the disease is urgently needed. Similarly, the identification and the implementation of clinical and laboratory parameters strongly correlated with the endoscopic activity, such as clinical scores, to better follow-up these patients, appear to be of relevance^[75]. Consequently, it is advisable that the aforementioned shift from a symptoms-based to a mucosa-based approach in the management of UC patients would not result in a trend to over-scope and/or over-treat patients for the achievement of MH. Indeed, because more solid evidence will be available regarding the role of MH, a rational approach to UC patients should reserve close monitoring and more potent therapies for “high-risk” patients, overcoming the dualism between symptom- and mucosa-targeted approaches and focusing increasingly on a “patient-based” approach.

REFERENCES

- 1 **Ordás I**, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012; **380**: 1606-1619 [PMID: 22914296 DOI: 10.1016/S0140-6736(12)60150-0]
- 2 **Halpin SJ**, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2012; **107**: 1474-1482 [PMID: 22929759 DOI: 10.1038/ajg.2012.260]
- 3 **Zallot C**, Peyrin-Biroulet L. Deep remission in inflammatory bowel disease: looking beyond symptoms. *Curr Gastroenterol Rep* 2013; **15**: 315 [PMID: 23354742 DOI: 10.1007/s11894-013-0315-7]
- 4 **Lewis JD**. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. *Gastroenterology* 2011; **140**: 1817-1826.e2 [PMID: 21530748]
- 5 **D'Haens G**, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lémann M, Marteau P, Rutgeerts P, Schölmmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; **132**: 763-786 [PMID: 17258735 DOI: 10.1053/j.gastro.2006.12.038]
- 6 **D'haens G**, Van Deventer S, Van Hogezaand R, Chalmers D, Kothe C, Baert F, Braakman T, Schaible T, Geboes K, Rutgeerts P. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. *Gastroenterology* 1999; **116**: 1029-1034 [PMID: 10220494 DOI: 10.1016/S0016-5085(99)70005-3]
- 7 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340**: 1398-1405 [PMID: 10228190 DOI: 10.1056/NEJM199905063401804]
- 8 **Rutgeerts P**, D'Haens G, Targan S, Vasiliasauskas E, Hanauer SB, Present DH, Mayer L, Van Hogezaand RA, Braakman T, DeWoody KL, Schaible TF, Van Deventer SJ. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117**: 761-769 [PMID: 10500056 DOI: 10.1016/S0016-5085(99)70332-X]
- 9 **Triantafyllidis JK**, Merikas E, Georgopoulos F. Current and emerging drugs for the treatment of inflammatory bowel disease. *Drug Des Devel Ther* 2011; **5**: 185-210 [PMID: 21552489]
- 10 **Rutgeerts P**, Vermeire S, Van Assche G. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? *Gut* 2007; **56**: 453-455 [PMID: 17369375 DOI: 10.1136/gut.2005.088732]
- 11 **Neurath MF**, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012; **61**: 1619-1635 [PMID: 22842618 DOI: 10.1136/gutjnl-2012-302830]
- 12 **Kornbluth A**, Sachar DB. Ulcerative colitis practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 1997; **92**: 204-211 [PMID: 9040192]
- 13 **Cosnes J**, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]
- 14 **Ha C**, Ullman TA, Siegel CA, Kornbluth A. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. *Clinical gastroenterology and hepatology*. AGA 2012; **10**: 1002-1007; quiz e1078
- 15 **Rogler G**, Vavricka S, Schoepfer A, Lakatos PL. Mucosal healing and deep remission: what does it mean? *World J Gastroenterol* 2013; **19**: 7552-7560 [PMID: 24282345 DOI: 10.3748/wjg.v19.i43.7552]
- 16 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048 [PMID: 13260656 DOI: 10.1136/bmj.2.4947.1041]
- 17 **Baron JH**, Connell AM, Lennard-jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964; **1**: 89-92 [PMID: 14075156 DOI: 10.1136/bmj.1.5375.89]
- 18 **Powell-Tuck J**, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses

- for active proctocolitis. *Scand J Gastroenterol* 1978; **13**: 833-837 [PMID: 364626 DOI: 10.3109/00365527809182199]
- 19 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629 [PMID: 3317057 DOI: 10.1056/NEJM198712243172603]
 - 20 **Sutherland LR**, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, Martin T, Sparr J, Prokipchuk E, Borgen L. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987; **92**: 1894-1898 [PMID: 3569765]
 - 21 **Rachmilewitz D**. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989; **298**: 82-86 [PMID: 2563951 DOI: 10.1136/bmj.298.6666.82]
 - 22 **Feagan BG**, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Dubé R, Cohen A, Steinhart AH, Landau S, Aguzzi RA, Fox IH, Vandervoort MK. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N Engl J Med* 2005; **352**: 2499-2507 [PMID: 15958805 DOI: 10.1056/NEJMoa042982]
 - 23 **D'Haens G**, Hommes D, Engels L, Baert F, van der Waaij L, Connor P, Ramage J, Dewit O, Palmén M, Stephenson D, Joseph R. Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. *Aliment Pharmacol Ther* 2006; **24**: 1087-1097 [PMID: 16984503 DOI: 10.1111/j.1365-2036.2006.03082.x]
 - 24 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lémann M, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Bernhardt CA, Mary JY, Sandborn WJ. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012; **61**: 535-542 [PMID: 21997563 DOI: 10.1136/gutjnl-2011-300486]
 - 25 **Warner B**, Harris AW. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **143**: e42; author reply e42 [PMID: 22634354]
 - 26 **Feagan BG**, Sandborn WJ, D'Haens G, Pola S, McDonald JW, Rutgeerts P, Munkholm P, Mittmann U, King D, Wong CJ, Zou G, Donner A, Shackleton LM, Gilgen D, Nelson S, Vandervoort MK, Fahmy M, Loftus EV, Panaccione R, Travis SP, Van Assche GA, Vermeire S, Levesque BG. The role of centralized reading of endoscopy in a randomized controlled trial of mesalazine for ulcerative colitis. *Gastroenterology* 2013; **145**: 149-157.e2 [PMID: 23528626]
 - 27 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Schnell P, Bernhardt CA, Mary JY, Sandborn WJ. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* 2013; **145**: 987-995 [PMID: 23891974 DOI: 10.1053/j.gastro.2013.07.024]
 - 28 **Samuel S**, Bruining DH, Loftus EV, Thia KT, Schroeder KW, Tremaine WJ, Faubion WA, Kane SV, Pardi DS, de Groen PC, Harmsen WS, Zinsmeister AR, Sandborn WJ. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol* 2013; **11**: 49-54.e1 [PMID: 22902762]
 - 29 **Peyrin-Biroulet L**, Bressenot A, Kampman W. Histologic Remission: The Ultimate Therapeutic Goal in Ulcerative Colitis? *Clin Gastroenterol Hepatol* 2013; Epub ahead of print [PMID: 23911875]
 - 30 **Korelitz BI**, Sommers SC. Response to drug therapy in Crohn's disease: evaluation by rectal biopsy and mucosal cell counts. *J Clin Gastroenterol* 1984; **6**: 123-127 [PMID: 6143776 DOI: 10.1097/00004836-198404000-00005]
 - 31 **Wright R**, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. *Am J Dig Dis* 1966; **11**: 847-857 [PMID: 5953695 DOI: 10.1007/BF02233941]
 - 32 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095 DOI: 10.1056/NEJMoa050516]
 - 33 **Yamamoto T**, Umegae S, Matsumoto K. Mucosal healing in patients with ulcerative colitis during a course of selective leukocytapheresis therapy: a prospective cohort study. *Inflamm Bowel Dis* 2010; **16**: 1905-1911 [PMID: 20310015 DOI: 10.1002/ibd.21260]
 - 34 **Ardizzone S**, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, Marmo R, Massari A, Molteni P, Maconi G et al: Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *AGA* 2011; **9**: 483-489; e483
 - 35 **Frøslie KF**, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]
 - 36 **Solberg IC**, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, Bernklev T, Henriksen M, Sauar J, Vatn MH, Moum B. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009; **44**: 431-440 [PMID: 19101844 DOI: 10.1080/00365520802600961]
 - 37 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID: 21723220 DOI: 10.1053/j.gastro.2011.06.054]
 - 38 **Margagnoni G**, Pagnini C, Menasci F, Festa S, Delle Fave G. Critical review of the evidence on 5-aminosalicylate for chemoprevention of colorectal cancer in ulcerative colitis: a methodological question. *Curr Clin Pharmacol* 2014; **9**: 84-90 [PMID: 24218994]
 - 39 **Actis GC**, Pellicano R, David E, Sapino A. Azathioprine, mucosal healing in ulcerative colitis, and the chemoprevention of colitic cancer: a clinical-practice-based forecast. *Inflamm Allergy Drug Targets* 2010; **9**: 6-9 [PMID: 19906011 DOI: 10.2174/187152810791292863]
 - 40 **Bitton A**, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, Ransil B, Wild G, Cohen A, Edwardes MD, Stevens AC. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. *Gastroenterology* 2001; **120**: 13-20 [PMID: 11208709 DOI: 10.1053/gast.2001.20912]
 - 41 **Bessissow T**, Lemmens B, Ferrante M, Bisschops R, Van Steen K, Geboes K, Van Assche G, Vermeire S, Rutgeerts P, De Hertogh G. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. *Am J Gastroenterol* 2012; **107**: 1684-1692 [PMID: 23147523 DOI: 10.1038/ajg.2012.301]
 - 42 **Lemmens B**, Arijs I, Van Assche G, Sagaert X, Geboes K, Ferrante M, Rutgeerts P, Vermeire S, De Hertogh G. Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 1194-1201 [PMID: 23518809 DOI: 10.1097/MIB.0b013e318280e75f]
 - 43 **Reinisch W**, Sandborn WJ, Panaccione R, Huang B, Pollack PF, Lazar A, Thakkar RB. 52-week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. *Inflamm Bowel Dis* 2013; **19**: 1700-1709 [PMID: 23665965]
 - 44 **Feagan BG**, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A. Vedolizumab as

- induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; **369**: 699-710 [PMID: 23964932 DOI: 10.1056/NEJMoa1215734]
- 45 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johans J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Hibi T, Rutgeerts P. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 85-95; quiz e14-15 [PMID: 23735746 DOI: 10.1053/j.gastro.2013.05.048]
- 46 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johans J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Rutgeerts P. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 96-109.e1 [PMID: 23770005]
- 47 **Jewell DP**, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. *Br Med J* 1974; **4**: 627-630 [PMID: 4441827 DOI: 10.1136/bmj.4.5945.627]
- 48 **Paoluzi OA**, Pica R, Marcheggiano A, Crispino P, Iacopini F, Iannoni C, Rivera M, Paoluzi P. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002; **16**: 1751-1759 [PMID: 12269968 DOI: 10.1046/j.1365-2036.2002.01340.x]
- 49 **Ardizzone S**, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47-53 [PMID: 15972298 DOI: 10.1136/gut.2005.068809]
- 50 **Panaccione R**, Ghosh S, Middleton S. Infliximab, azathioprine, or infliximab azathioprine for treatment of moderate to severe ulcerative colitis: the UC SUCCESS trial. ECCO meeting 2011: A-13
- 51 **Rutgeerts PJ**. Review article: the limitations of corticosteroid therapy in Crohn's disease. *Aliment Pharmacol Ther* 2001; **15**: 1515-1525 [PMID: 11563990 DOI: 10.1046/j.1365-2036.2001.01060.x]
- 52 **Lee FI**, Jewell DP, Mani V, Keighley MR, Kingston RD, Record CO, Grace RH, Daniels S, Patterson J, Smith K. A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. *Gut* 1996; **38**: 229-233 [PMID: 8801202 DOI: 10.1136/gut.38.2.229]
- 53 **Löfberg R**, Danielsson A, Suhr O, Nilsson A, Schiöler R, Nyberg A, Hultcrantz R, Kollberg B, Gillberg R, Willén R, Persson T, Salde L. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology* 1996; **110**: 1713-1718 [PMID: 8964395 DOI: 10.1053/gast.1996.v110.pm8964395]
- 54 **Mulder CJ**, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. 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**: 549-553 [PMID: 8823568 DOI: 10.1097/00042737-199606000-00010]
- 55 **Marshall JK**, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. *Gut* 1997; **40**: 775-781 [PMID: 9245932 DOI: 10.1136/gut.40.6.775]
- 56 **Rizzello F**, Gionchetti P, D'Arienzo A, Manguso F, Di Matteo G, Annese V, Valpiani D, Casetti T, Adamo S, Prada A, Castiglione GN, Varoli G, Campieri M. Oral beclomethasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002; **16**: 1109-1116 [PMID: 12030952 DOI: 10.1046/j.1365-2036.2002.01298.x]
- 57 **Campieri M**, Adamo S, Valpiani D, D'Arienzo A, D'Albasio G, Pitzalis M, Cesari P, Casetti T, Castiglione GN, Rizzello F, Manguso F, Varoli G, Gionchetti P. Oral beclomethasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003; **17**: 1471-1480 [PMID: 12823149 DOI: 10.1046/j.1365-2036.2003.01609.x]
- 58 **Gionchetti P**, D'Arienzo A, Rizzello F, Manguso F, Maieron R, Lecis PE, Valpiani D, Iaquinio G, Annese V, Balzano A, Varoli G, Campieri M. Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalamine: a single-blind randomized controlled trial. *J Clin Gastroenterol* 2005; **39**: 291-297 [PMID: 15758622 DOI: 10.1097/01.mcg.0000155124.74548.61]
- 59 **Gross V**, Bar-Meir S, Lavy A, Mickisch O, Tulassay Z, Protnai L, Kupcinkas L, Kiudelis G, Pokrotnieks J, Kovács A, Faszczyk M, Razbadauskas A, Margus B, Stolte M, Müller R, Greinwald R. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther* 2006; **23**: 303-312 [PMID: 16393311 DOI: 10.1111/j.1365-2036.2006.02743.x]
- 60 **Manguso F**, Balzano A. Meta-analysis: the efficacy of rectal beclomethasone dipropionate vs. 5-aminosalicylic acid in mild to moderate distal ulcerative colitis. *Aliment Pharmacol Ther* 2007; **26**: 21-29 [PMID: 17555418 DOI: 10.1111/j.1365-2036.2007.03349.x]
- 61 **Travis SP**, Stange EF, Lémann M, Oresland T, Bemelman WA, Chowers Y, Colombel JF, D'Haens G, Ghosh S, Marteau P, Kruijs W, Mortensen NJ, Penninckx F, Gassull M. European evidence-based Consensus on the management of ulcerative colitis: Current management. *J Crohns Colitis* 2008; **2**: 24-62 [PMID: 21172195 DOI: 10.1016/j.crohns.2007.11.002]
- 62 **Römkens TE**, Kampschreur MT, Drenth JP, van Oijen MG, de Jong DJ. High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials. *Inflamm Bowel Dis* 2012; **18**: 2190-2198 [PMID: 22419617 DOI: 10.1002/ibd.22939]
- 63 **Kamm MA**, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, Lyne A, Stephenson D, Palmen M, Joseph RE. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007; **132**: 66-75; quiz 432-433 [PMID: 17241860 DOI: 10.1053/j.gastro.2006.10.011]
- 64 **Campieri M**, Lanfranchi GA, Bazzocchi G, Brignola C, Sarti F, Franzin G, Battocchia A, Labo G, Dal Monte PR. Treatment of ulcerative colitis with high-dose 5-aminosalicylic acid enemas. *Lancet* 1981; **2**: 270-271 [DOI: 10.1016/S0140-6736(81)90523-7]
- 65 **Kornbluth A**, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-23; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2009.727]
- 66 **Sutherland L**, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; **(2)**: CD000543 [PMID: 16625536]
- 67 **Sandborn WJ**, Hanauer S, Lichtenstein GR, Safdi M, Edeline M, Scott Harris M. Early symptomatic response and mucosal healing with mesalazine rectal suspension therapy in active distal ulcerative colitis—additional results from two controlled studies. *Aliment Pharmacol Ther* 2011; **34**: 747-756 [PMID: 21848857 DOI: 10.1111/j.1365-2036.2011.04800.x]
- 68 **Vecchi M**, Meucci G, Gionchetti P, Beltrami M, Di Maurizio P, Beretta L, Ganio E, Usai P, Campieri M, Fornaciari G, de Franchis R. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. *Aliment Pharmacol Ther* 2001; **15**: 251-256 [PMID: 11148445 DOI: 10.1046/j.1365-2036.2001.00913.x]
- 69 **Hanauer SB**. Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: results of a multicentered placebo-controlled trial. The U.S. PENTASA Enema Study Group. *Inflamm Bowel Dis* 1998; **4**: 79-83 [PMID: 9589293]
- 70 **Pokrotnieks J**, Marlicz K, Paradowski L, Margus B, Zaborowski P, Greinwald R. Efficacy and tolerability of mesala-

- zine foam enema (Salofalk foam) for distal ulcerative colitis: a double-blind, randomized, placebo-controlled study. *Aliment Pharmacol Ther* 2000; **14**: 1191-1198 [PMID: 10971236 DOI: 10.1046/j.1365-2036.2000.00784.x]
- 71 **Meucci G**, Fasoli R, Saibeni S, Valpiani D, Gullotta R, Colombo E, D'Incà R, Terpin M, Lombardi G. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. *Inflamm Bowel Dis* 2012; **18**: 1006-1010 [PMID: 21830282 DOI: 10.1002/ibd.21838]
- 72 **Langholz E**, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology* 1994; **107**: 3-11 [PMID: 8020674]
- 73 **Farmer RG**, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. *Dig Dis Sci* 1993; **38**: 1137-1146 [PMID: 8508710 DOI: 10.1007/BF01295733]
- 74 **Rungoe C**, Langholz E, Andersson M, Basit S, Nielsen NM, Wohlfahrt J, Jess T. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut* 2013; Epub ahead of print [PMID: 24056767 DOI: 10.1136/gutjnl-2013-305607]
- 75 **Dhanda AD**, Creed TJ, Greenwood R, Sands BE, Probert CS. Can endoscopy be avoided in the assessment of ulcerative colitis in clinical trials? *Inflamm Bowel Dis* 2012; **18**: 2056-2062 [PMID: 22271464 DOI: 10.1002/ibd.22879]

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