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Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus

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Short title: **Endoscopic response and remission in ulcerative colitis**

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Keywords

Ulcerative colitis, endoscopic indices, Mayo score, UCEIS.

Abbreviations:

Endoscopic Activity Index (EAI); inflammatory bowel disease (IBD); International Organization For the Study of Inflammatory Bowel Disease (IOIBD); ulcerative colitis (UC); Ulcerative Colitis Colonoscopic Index of Severity (UCCIS); Ulcerative Colitis Endoscopic Index of Severity (UCEIS).

Abstract

Background. Recently, endpoints for clinical trials have been changing from measuring clinical response to mucosal healing in ulcerative colitis (UC). Endoscopic evaluation is the current gold standard to assess mucosal lesions and has become a major measure of therapeutic efficacy in addition to patients reported outcomes.

Aim. To achieve consensus on endoscopic definitions of remission and response for UC clinical trials.

Methods. In reaching the current international recommendations on an International Organization For the Study of Inflammatory Bowel Disease (IOIBD) initiative, we first performed a systematic review of technical aspects of endoscopic scoring systems. Then, to achieve consensus on endoscopic definitions of remission and response for clinical trials, we conducted a two-round vote using a Delphi-style process among fifteen specialists in the field of inflammatory bowel diseases.

Results. The literature review showed that many endoscopic indices have been proposed to evaluate disease activity in UC; most are un-validated and arbitrary definitions have been used in clinical trials for defining endoscopic response or remission. At the end of the voting process the investigators ranked first UCEIS 0 for the definition of endoscopic remission, and a decrease in Mayo endoscopic score ≥1 grade or a decrease in UCEIS ≥ 2 points for the definition of endoscopic response in UC.

Conclusion. These international recommendations represent the first consensus on measurement indices for endoscopic outcomes in UC. They should be subject to prospective testing in clinical trials of UC.

Introduction

Accumulating evidence indicates that mucosal healing is associated with better outcomes during the course of ulcerative colitis (UC) including decreased need for colectomy, reduced rates of hospitalization and increased rate of steroid-free remission[1]. The absence of endoscopic healing is associated with an increased risk of dysplasia and colorectal cancer[1]. As recent advances in the medical therapy of inflammatory bowel diseases (IBD) have made mucosal healing a realistic goal, endoscopic indices are increasingly used both in clinical trials and practice.

Many scoring systems have been developed in UC to evaluate endoscopic disease activity, but none has yet had all properties fully assessed. As a consequence, most studies addressing mucosal healing have used arbitrary definitions for endoscopic response or remission. Required qualities of any instrument are the following:

- *reproducibility* (does the instrument produce the same or similar results in individuals on different occasions or by different observers?)
- *validity* (does the instrument measure what is intended?),
- *responsiveness* or sensitivity-to-change (is the instrument able to measure change in an individual when it does occur?).

We achieved an international consensus on definitions of endoscopic response and remission in UC through a two-step process. The purpose of this paper on the International Organization For the Study of Inflammatory Bowel Disease (IOIBD) initiative was first to review technical aspects of scoring systems for UC (available indices, definitions, construction, strengths and weaknesses), and then to develop a consensus definition among experts in the field of IBD regarding endoscopic response and remission in UC, using a Delphi-style process.

Available endoscopic scoring systems for UC (table 1)

First scores

The first description of endoscopic features in UC was reported by Truelove and Witts in 1955[2]. In this landmark randomized controlled trial of hydrocortisone therapy, sigmoidoscopic findings were classified at the end of the treatment course as normal or near normal (slight hyperaemia or slight granularity), improved, unchanged or worse, based on the physician's global evaluation. A pioneer work was performed introducing the Baron score in 1964[3], followed by a host of other scores, Sutherland *et al*.,[4] Feagan et al,[5] Matts et al.,[6] Blackstone et al.,[7] Rachmilewitz et al.[8] Descriptions and properties of these scores are presented in details in the supplementary material (S1). None of these scores have been validated.

The Mayo Clinic score and its endoscopic sub-score

Definition

Schroeder *et al*.[9] performed serial flexible proctosigmoidoscopic assessments during a placebo-controlled trial of oral delayed release mesalamine[9]. They defined *a priori* an endoscopic sub-score ranging from 0 to 3 with the following characteristics for grading:

normal or inactive disease (0);

mild disease (erythema, decreased vascular pattern, mild friability) (1);

moderate disease (marked erythema, absent vascular pattern, friability, erosions) (2),

severe disease (spontaneous bleeding, ulceration) (3). [9]

The descriptors were not precisely defined and, like the original Baron score, there was overlap between descriptors used for different grades. In order to improve clarity, several randomized controlled trials[10–12] have used a modification to exclude any friability from grade

(1). Friability has subsequently been defined as the presence of bleeding following gentle contact with the endoscope during insertion.[13]

Strengths and weaknesses

The Mayo score has been the most commonly used in clinical trials until now (2016), but it has not been validated. It does, however, show good reproducibility between experienced observers.[13,14] In the same study[13] that evaluated performance characteristics of the modified Baron score among 7 IBD specialists reading 50 videosigmoidoscopies, the intraclass correlation coefficient was 0.79, known to be equivalent to a weighted kappa statistic using square distance weights, a tool that overestimates agreement by giving much too important contribution of large disagreements to agreement, when compared to standard unweighted Kappa.[15] In another study,[16] good concordance for the Mayo Clinic endoscopy subscore was shown between experienced endoscopists, but not among trainee endoscopists. However, there was a major methodological pitfall, since the kappa value between the ratings of experienced and trainee endoscopists used a gold standard defined as the mean of the evaluations of experienced endoscopists. The responsiveness of the modified Mayo score has also been quantified and shown to be poor, with a Guyatt's responsiveness measure and Cohen's effect size of 0.32 and 0.49, respectively.[17] Part of the problem is the limitations imposed by a 4 grade scale.

Osada *et al*.[14] therefore proposed a modification of the Mayo endoscopic subscore to a 6 grade scale: normal or inactive disease, ramifying vascular pattern clearly visible (1); mild erythema, decreased vascular pattern (2); marked erythema, absent vascular pattern, oedema, friability or granularity of mucosa (3); erosions, small ulcers <4mm, with regenerating epithelium (4); active ulcers, fewer than 10 per 10 cm segment (5); multiple and deep ulcers, ≥5mm, more than 10 per 10 cm segment (6). The reproducibility of their "modified 6 point

activity score", was comparable to those observed for the Baron, Matts, Blackstone and Mayo scores, with a weighted kappa of 0.65 among specialists and 0.54 among trainees.[14]

Recent developments

Endoscopic Activity Index (EAI)

Definition

The EAI [18] was designed to facilitate decision-making when treating severe UC. The score has 6 descriptors, each with a level increasing from 0 to 2 or 3 according to severity: ulcer size (3), ulcer depth (3), redness (2), bleeding (3), mucosal oedema (3), mucus exudate (2). The value given to each of these lesions was decided arbitrarily and not derived from statistical analysis. Pictures of typical endoscopic appearances for each level are provided in the publication.

Strengths and weaknesses

Results from applying the EAI in videosigmoidoscopies from 396 patients with UC were correlated with those obtained using the Matts, Rachmilewitz and Lichtiger scores of disease activity. The latter is solely a clinical activity index, although widely used in trials of severe UC. Notably, there was a fairly wide range of EAI scores for those patients with the highest Matts' or Rachmilewitz endoscopic score, suggesting that the EAI could provide a more precise grading of severe lesions[18]. Colonoscopies were repeated within 30 days in 25 patients to evaluate treatment efficacy. The relationship between changes in the clinical activity (Lichtiger) index and endoscopic scores was evaluated. The median EAI was shown to change significantly in those who achieved clinical remission (n=8/25) and in those who responded to medical treatment (n=10/25), but not in those who had no response (n=7/25), while neither the Matt's nor Rachmilewitz scores were as sensitive to change.[18] The authors

did not use standard tools to assess responsiveness and the very limited sample size render results open to question

Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)

Definition

Thia *et al*. from the Mayo Clinic developed a full colonoscopy severity index, the UCCIS[19,20]. Colonoscopy videos from 51 patients were assessed by 7 gastroenterologists, segment by segment (cecum/ascending, transverse, descending, sigmoid, rectum), for 10 *a priori* defined descriptors which were scored between 0 and 2, 3 or 4 for specific descriptors, as well as for segmental endoscopic severity (4-point scale) and global endoscopic severity (4-point scale and a 10-cm visual analogue scale). Inter-observer agreement for the 10 descriptors, segmental and global assessment of endoscopic severity was studied. The UCCIS was then derived from multivariate regression modelling of segmental assessment of endoscopic severity as a function of descriptor scores, with coefficients averaged across segments and then approximated for simplification. The UCCIS is calculated as the weighted sum over each segment of four descriptors (weighting in brackets): granularity (3.6), vascular pattern (3.1), ulceration (3.5) and bleeding/friability (2.5) [19,20].

Strengths and weaknesses

In its final version, the UCCIS accounted for 85% of the variation between observers in their assessment of global endoscopic severity using the visual analogue scale ($p<0.001$)[19]. Inter-observer agreement for scoring descriptors was assessed using Lin's concordance correlation coefficient, a tool with the same limitations as the intraclass correlation coefficient (above). The estimates of agreement were similar for granularity, vascular pattern and ulceration (between 0.55 and 0.77 across segments), but lower for bleeding/friability (between 0.34 and

0.66). In a second study on a different set of 50 patients, the authors confirmed the good inter-observer agreement for the descriptors involved in the UCCIS with the global assessment of endoscopic severity[20]. The concordance correlation coefficients varied between 0.70 and 0.85 across segments for granularity, vascular pattern and ulceration, but between 0.56 and 0.77 for bleeding/friability[20] (as was observed in the study developing the UCEIS[21]). The UCCIS was validated on this new sample, accounting for 80% of the variation in the overall assessment of severity using the visual analogue scale. Sensitivity to change after a treatment with known efficacy has yet to be evaluated.

Ulcerative colitis Endoscopic Index of Severity (UCEIS)

Definition

The UCEIS[21,22] was developed from a two-phase study using a library of 670 videosigmoidoscopies from trials of mild-moderately active UC (total Mayo Clinic scores 0-11), augmented by 10 videos from 5 people without UC and 5 hospitalised patients with acute severe UC.[23] (see online supplementary material 2-S2 for phase 1 and phase 2 UCEIS construction).

Because the original score had assigned '1' to normality for each descriptor, the original range of the UCEIS was 3-11, so the assignment of levels was rebased to zero without any other change in the descriptors (UCEIS score 0-8[22]): (1) vascular pattern scored 0 to 2, (2) bleeding scored 0 to 3, and (3) erosions and ulcers scored 0 to 3.

Strengths and weaknesses

The 57 videos aligned to a range on the 100 point visual analogue scale of 4-94, indicating that the videos appropriately captured the full range of endoscopic severity of UC[22]. There was a high level of correlation between UCEIS scores and overall assessment of severity on

visual analogue scale (correlation coefficient, 0.93). The inter-investigator reliability ratio for overall assessment of severity was 0.84, and for UCEIS was 0.88. Inter-investigator agreement in determination of UCEIS scores was, however, moderate (weighted kappa 0.50, using weights of 1 for agreement, 0.5 for differences by 1 level, 0 otherwise), with descriptors ranging from a standard kappa value of 0.48 (for bleeding) to 0.54 (for vascular pattern). In a subsequent study using 40 new videos and 40 different readers, (20 blinded to clinical information knowledge, 20 un-blinded), inter-investigator agreement in determination of UCEIS scores was similar (weighted kappa value of 0.47), with descriptors ranging from a standard kappa of 0.40 and 0.44 (for bleeding among blinded and un-blinded readers) to 0.50 and 0.53 (for vascular pattern among blinded and un-blinded readers). Knowledge of clinical information had no impact on scoring the UCEIS[24].

The evaluation of the UCEIS has also been shown to be reproducible among 7 IBD specialists reading 50 videosigmoidoscopies of patients with mildly-to-moderately active UC (intraclass correlation coefficient of 0.83, with the limitations indicated above).[13] Using data from a randomized trial comparing mesalamine and placebo in mildly-to-moderately active UC, central reading provided a consistently lower absolute treatment effect in the placebo group compared to local investigators, resulting in a greater treatment effect between the placebo and active treatment groups[13]. The responsiveness of the UCEIS was quantified using these videos, with a Guyatt's responsiveness measure and Cohen's effect size of 0.49 and 0.58, respectively. Although numerically higher than those observed for the modified Baron's score or modified Mayo endoscopic sub-score (above), responsiveness of the UCEIS remains to be fully defined.[17] A Japanese group have compared the responsiveness of the UCEIS with the Mayo endoscopic subscore in a retrospective study of 41 patients treated with tacrolimus.[25] The mean UCEIS improved from 6.2 ± 0.9 to 3.4 ± 2.1 ($p<0.001$), but the pre- and post-treatment Mayo scores were not significantly different, probably because it could not

discriminate on the size of ulcers, so a proportion of patients still scored 3 after treatment[25]. Segmental variation in UCEIS scoring has been examined,[26,27] but the simplicity of the three-descriptor index applied to the most severely affected area at flexible sigmoidoscopy is appealing.

In conclusion, the new scores, especially the UCEIS, have been constructed using a much more rigorous methodology than earlier indices. This represents progress although the indices have not been validated in all dimensions and have not been fully evaluated in terms of sensitivity to change. What matters is that endoscopists use a common language when describing the endoscopic severity of UC, both in clinical trials and clinical practice.

Endoscopic remission and response in UC clinical trials (Table 2)

The definitions of endoscopic remission and response in UC lacks consistency between clinical trials[2,12,28–67], takes no account of inter-observer variation in endoscopic scoring, and with rare exceptions have not been related to future outcome. It is hardly surprising that this has an impact on outcomes with regulatory implications[13]. This is illustrated by the comprehensive table of definitions for endoscopic remission and response in UC clinical trials provided in this review (table 2).

International consensus for endoscopic definitions of remission and response in ulcerative colitis clinical trials

Methods

In order to establish a consensus for defining endoscopic remission and response in UC we performed a vote using a Delphi-style process[68]. The first step consisted of a literature review. A systematic search in databases (Pubmed, Medline, Embase) and international congress abstracts was performed, from which definitions of endoscopic outcome parameters for remission and response in UC trials were extracted (table 2). The eligibility criteria of studies were: studies published in English between 1955 and 2014; randomized controlled trials, clinical controlled trials, open label studies; studies with a population of 10 or more patients; studies with subjects 18 years of age and older; studies including patients with ulcerative colitis. A total of 15 specialists in the field of IBD, 11 of them among the IOIBD, from 9 countries from Western Europe, North America and Australia participated in the process, which was conducted through an internet survey. All of them were provided with the results of the systematic review. At each step of the process, participants were blinded to the votes of others. For the first round of the vote, each of the 15 specialists was asked to rate the importance of the selected outcome measurements for endoscopic remission and endoscopic response. After analysis of the results by the investigators, the four definitions with the highest median rank were selected and ordered by increasing median rank. In case of equal median rank, the definitions were ordered by increasing mean rank (figure 1). In the second round of the vote, each Delphi panellist received a questionnaire that included these four definitions, with the first round's median rank and histogram of each definition summarized by the investigators. Specialists were again asked to rank-order the four definitions. Finally, for each definition, the proposition with the highest median rank was selected. In addition to median and mean rank, the proportion of specialists who ranked each definition first and first or second were given.

Secondly, in order to exclude the potential bias of UCEIS vs Mayo endoscopic score specialists' personal preferences due to their geographic origins, we compared votes' results of European vs North America experts.

Results

After the specialist panel opinion, eight definitions were retained for endoscopic remission in UC, and five definitions were retained for endoscopic response in UC, for the vote (table 3).

For the eight proposed definitions of endoscopic remission in UC (table 3), the four definitions with the highest rank on the first round of the vote, by increasing mean rank, were (figure 1): (1) UCEIS 0; (2) Mayo endoscopic subscore 0; (3) UCEIS≤1; (4) Mayo endoscopic subscore ≤1. After the second round of the Delphi style process, *UCEIS 0* ranked first, with the highest median rank (median 1, mean 1.6).

Regarding the five definitions of endoscopic response in UC (table 3), the four definitions with the highest rank after the first vote, by increasing mean rank, were: (1) decrease in Mayo endoscopic score ≥1 grade; (2) decrease in UCEIS ≥ 2 points; (3) decrease in UCEIS ≥ 2 point or UCEIS = 0; (4) decrease in UCEIS ≥ 1 point. After the second round of the global voting, two definitions were ranked *ex aequo* with equal median rank of 2, almost equal mean rank, and a high proportion of investigators ranking them 1 or 2 (respectively 0.87 and 0.60): *decrease in UCEIS ≥ 2 points* (median 2, mean 1.93) and *decrease in Mayo endoscopic score ≥1 grade* (median 2, mean 2.07).

In the European vs North America comparison, the selection at the first round of the vote, and the two first ranks at the second round were the same among European and American endoscopists (see online supplementary material 3-S3).

Discussion

For remission and response in UC, numerous scores and indices have been proposed over the past thirty years. The Mayo Clinic endoscopic sub score, first published in 1987,[9] is still the one most used in clinical trials, as well as in endoscopic rooms worldwide. In order to decrease the very wide variation in endoscopic interpretation of UC disease severity between specialists, the UCEIS has recently been elaborated and further validated.[21,22] These two scores were ranked first and/or second by the IOIBD group for endoscopic definitions of remission and response, with a preference for the UCEIS 0 for endoscopic remission, albeit that there are only preliminary data on specific reproducibility of UCEIS 0, and needs further assessment. The UCEIS is currently the most validated tool for assessing the endoscopic severity of UC. Nevertheless, further studies are required to establish thresholds, the clinical relevance of different UCEIS scores, and to explore more deeply its sensitivity to change.

It should be acknowledged that when both the Mayo Clinic endoscopic subscore and the UCEIS are performed by qualified blinded central readers, the kappa values are similar.[13] Training endoscopists on precise definitions and the scoring of the lesions, as well as calculating endoscopic indices is essential before using the scores in clinical trials. A training tool for the UCEIS is freely available on line (www.e-learning.ecco-ibd.eu). It should also be recognised that the role of central reading in randomized controlled trials for CD and UC is crucial; it has become clear that the choice of combined clinical and endoscopic outcome criteria leads to a reduction in placebo responses[69], especially when central reading of the endoscopic records is performed.[13]

It was notable that both UCEIS 0 and Mayo Clinic endoscopic subscore 0 had higher median ranks in both rounds of voting, compared to UCEIS or Mayo Clinic endoscopic subscore ≤ 1, even though clinical trials to date have defined endoscopic mucosal healing as a (modified)

Mayo Clinic endoscopic subscore ≤1. That reflects the direction of travel in trial design to reduce the placebo rate of remission and to raise the expectations for patients. Patients with a Mayo endoscopic subscore 1 have been shown to have a higher risk of relapse in the following year than those with Mayo endoscopic subscore 0, regardless of the extent of disease. In the *post hoc* analysis of infliximab trials, a Mayo endoscopic subscore of 0 discriminated from a score of 1 with regard to symptoms and steroid-dependency, although not colectomy: an endoscopic sub-score of 0 at week 8 predicted symptom relief (stool frequency or 1-2 more than normal each day, but no rectal bleeding) at weeks 30 and 54 in 71% and 74% respectively, compared to 51% and 47% for a score of 1 at week 8.[70] Patients with an endoscopic subscore of 0 at week 8 in the ACT 1 trial had a higher rate of steroid-free remission at week 54 (63%, 22/32) than those with a score of 1 (46%, 25/54).[46] In a prospective study of 187 patients with endoscopic remission (Mayo subscore 0 or 1), 9% with Mayo subscore 0 relapsed during the first 6 months of follow up, compared to 37% with Mayo endoscopic subscore 1 ($p<0.001$).[71] Interestingly, preliminary work from Japan suggests that the UCEIS (0 vs 1 or 2) may be able to discriminate outcomes over 2 years in those with a Mayo endoscopic subscore 0.[72] Among 84 patients with a Mayo Clinic endoscopy subscore of 0, 19/20 (95%) of those with a UCEIS of 0 remained in remission for 23 months, compared to 48/64 (77%) with a UCEIS of 1 or 2.[72] Furthermore, in the referral center UC cohort in Nancy, France, in 55 patients with a Mayo endoscopic subscore of 0 or 1, 8/55 (15%) came to colectomy during a median follow-up of 48 months, all with a Mayo endoscopic subscore of 1 at first evaluation[73]. Comparing survival curves, a Mayo endoscopic subscore of 0 was associated with a lower rate colectomy than a subscore of 1 ($p=0.05$).[73] A UCEIS score of 0 or Mayo endoscopic subscore 0 seems the appropriate therapeutic target for patients with UC if one aims to change disease course, and histological healing may represent the ultimate therapeutic goal.[74]

After reviewing technical aspects of available indices in UC through a Delphi-style process, international specialists have agreed on recommendations for endoscopic definitions of remission and response in clinical trials (evidence level 3, grade of recommendation C):

Statement 1: definition of endoscopic remission is UCEIS 0.

Statement 2: definition of endoscopic response is a decrease in Mayo endoscopic subscore ≥1 grade or decrease in UCEIS ≥ 2 points.

These definitions and recommendations should be subject to prospective testing in clinical trials of UC.

References

1. Peyrin-Biroulet L, Ferrante M, Magro F, et al. Results from the 2nd Scientific Workshop of the ECCO. I: Impact of mucosal healing on the course of inflammatory bowel disease. J Crohns Colitis 2011;5:477–483.
2. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2:1041–1048.
3. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J 1964;1:89–92.
4. Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology 1987;92:1894–1898.
5. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med 2005;352:2499–2507.
6. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. Q J Med 1961;30:393–407.
7. Blackstone MO. Differentiating ulcerative colitis from Crohn's disease. In: *Endoscopic interpretation: normal and pathologic appearance of the gastrointestinal tract*. Raven. New York: Blackstone MO; 1984:464–96.
8. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ 1989;298:82–86.
9. 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.
10. 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;137:1934-1943–3.
11. Kamm MA, Lichtenstein GR, Sandborn WJ, et al. Effect of extended MMX mesalamine therapy for acute, mild-to-moderate ulcerative colitis. Inflamm Bowel Dis 2009;15:1–8.
12. Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of once- or twice-daily MMX

mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. Clin Gastroenterol Hepatol 2007;5:95–102.
13. Feagan BG, Sandborn WJ, D'Haens G, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology 2013;145:149–157.
14. Osada T, Ohkusa T, Yokoyama T, et al. Comparison of several activity indices for the evaluation of endoscopic activity in UC: inter- and intraobserver consistency. Inflamm Bowel Dis 2010;16:192–197.
15. Marteau P, Laharie D, Colombel J-F, et al. Interobserver Variation Study of the Rutgeerts Score to Assess Endoscopic Recurrence after Surgery for Crohn's Disease. J Crohns Colitis 2016;10:1001–1005.
16. Lange T de, Larsen S, Aabakken L. Inter-observer agreement in the assessment of endoscopic findings in ulcerative colitis. BMC Gastroenterol 2004;4:9.
17. B.G. Levesque, E.V. Loftus, R. Panaccione, J.W. McDonald, G. Van Assche, G. Zou, L. Stitt, R. Khanna, W.J. Sandborn, G. D'Haens, M.K. Vandervoort, B.G. Feagan. Responsiveness of endoscopic indices in the evaluation of ulcerative colitis. J Crohns Colitis 2014; 8:S124.
18. Naganuma M, Ichikawa H, Inoue N, et al. Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients. J Gastroenterol 2010;45:936–943.
19. Thia KT, Loftus EV Jr, Pardi DS, et al. Measurement of disease activity in ulcerative colitis: interobserver agreement and predictors of severity. Inflamm Bowel Dis 2011;17:1257–1264.
20. Samuel S, Bruining DH, Loftus EV Jr, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clin Gastroenterol Hepatol 2013;11:49–54.
21. Travis SPL, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut 2012;61:535–542.
22. Travis SP, Schnell D, Krzeski P, et al. Reliability and Initial Validation of the Ulcerative Colitis Endoscopic Index of Severity. Gastroenterology 2013;145:987-95.
23. Travis S, Yap LM, Hawkey C, et al. RDP58 is a novel and potentially effective oral therapy for ulcerative colitis. Inflamm Bowel Dis 2005;11:713–719.
24. Travis SPL, Schnell D, Feagan BG, et al. The Impact of Clinical Information on the Assessment of Endoscopic Activity: Characteristics of the Ulcerative Colitis Endoscopic Index Of Severity [UCEIS]. J Crohns Colitis 2015;9:607–616.
25. Ikeya K, Hanai H, Sugimoto K, et al. The Ulcerative Colitis Endoscopic Index of Severity More Accurately Reflects Clinical Outcomes and Long-term Prognosis than the Mayo Endoscopic Score. J Crohns Colitis 2016;10:286–295.
26. Colombel J-F, Ordás I, Ullman T, et al. Agreement Between Rectosigmoidoscopy and Colonoscopy Analyses of Disease Activity and Healing in Patients With Ulcerative Colitis. Gastroenterology 2016;150:389–395.
27. Harris MS, Hartman D, Lemos BR, et al. AVX-470, an Orally Delivered Anti-Tumour Necrosis Factor Antibody for Treatment of Active Ulcerative Colitis: Results of a First-in-Human Trial. J Crohns Colitis 2016;10:631–640.
28. Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. Br Med J 1974;4:627–630.
29. Kam L, Cohen H, Dooley C, et al. A comparison of mesalamine suspension enema and oral sulfasalazine for treatment of active distal ulcerative colitis in adults. Am J Gastroenterol 1996;91:1338–1342.

30. Löfberg R, Danielsson A, Suhr O, et al. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. Gastroenterology 1996;110:1713–1718.
31. Lee FI, Jewell DP, Mani V, et al. A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. Gut 1996;38:229–233.
32. Kruis W, Brandes JW, Schreiber S, et al. Olsalazine versus mesalazine in the treatment of mild to moderate ulcerative colitis. Aliment Pharmacol Ther 1998;12:707–715.
33. Vernia P, Monteleone G, Grandinetti G, et al. Combined oral sodium butyrate and mesalazine treatment compared to oral mesalazine alone in ulcerative colitis: randomized, double-blind, placebo-controlled pilot study. Dig Dis Sci 2000;45:976–981.
34. Vecchi M, Meucci G, Gionchetti P, et al. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. Aliment Pharmacol Ther 2001;15:251–256.
35. D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001;120:1323–1329.
36. Green JRB, Mansfield JC, Gibson JA, et al. A double-blind comparison of balsalazide, 6.75 g daily, and sulfasalazine, 3 g daily, in patients with newly diagnosed or relapsed active ulcerative colitis. Aliment Pharmacol Ther 2002;16:61–68.
37. Mansfield JC, Giaffer MH, Cann PA, et al. A double-blind comparison of balsalazide, 6.75 g, and sulfasalazine, 3 g, as sole therapy in the management of ulcerative colitis. Aliment Pharmacol Ther 2002;16:69–77.
38. Levine DS, Riff DS, Pruitt R, et al. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. Am J Gastroenterol 2002;97:1398–1407.
39. Pruitt R, Hanson J, Safdi M, et al. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. Am J Gastroenterol 2002;97:3078–3086.
40. Rizzello F, Gionchetti P, D'Arienzo A, et al. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. Aliment Pharmacol Ther 2002;16:1109–1116.
41. Campieri M, Adamo S, Valpiani D, et al. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. Aliment Pharmacol Ther 2003;17:1471–1480.
42. Raedler A, Behrens C, Bias P. Mesalazine (5-aminosalicylic acid) micropellets show similar efficacy and tolerability to mesalazine tablets in patients with ulcerative colitis--results from a randomized-controlled trial. Aliment Pharmacol Ther 2004;20:1353–1363.
43. 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;100:2478–2485.
44. Marakhouski Y, Fixa B, Holomán J, et al. A double-blind dose-escalating trial comparing novel mesalazine pellets with mesalazine tablets in active ulcerative colitis. Aliment Pharmacol Ther 2005;21:133–140.
45. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805–1811.
46. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.

47. Gibson PR, Fixa B, Pekárková B, et al. Comparison of the efficacy and safety of Eudragit-L-coated mesalazine tablets with ethylcellulose-coated mesalazine tablets in patients with mild to moderately active ulcerative colitis. Aliment Pharmacol Ther 2006;23:1017–1026.
48. D'Haens G, Hommes D, Engels L, et al. 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.
49. 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.
50. 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 J Can Gastroenterol 2007;21:827–834.
51. Kamm MA, Lichtenstein GR, Sandborn WJ, et al. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. Gut 2008;57:893–902.
52. 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;103:3106–3114.
53. Kruis W, Kiudelis G, Rácz I, et al. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. Gut 2009;58:233–240.
54. Scherl EJ, Pruitt R, Gordon GL, et al. Safety and efficacy of a new 3.3 g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo-controlled study. Am J Gastroenterol 2009;104:1452–1459.
55. Barreiro-de Acosta M, Lorenzo A, Mera J, et al. Mucosal healing and steroid-sparing associated with infliximab for steroid-dependent ulcerative colitis. J Crohns Colitis 2009;3:271–276.
56. Afif W, Leighton JA, Hanauer SB, et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis 2009;15:1302–1307.
57. 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;60:780–787.
58. Gong Y, Zha Q, Li L, et al. Efficacy and safety of Fufangkushen colon-coated capsule in the treatment of ulcerative colitis compared with mesalazine: a double-blinded and randomized study. J Ethnopharmacol 2012;141:592–598.
59. Ogata H, Kato J, Hirai F, et al. Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. Inflamm Bowel Dis 2012;18:803–808.
60. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012;380:1909–1915.
61. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367:616–624.
62. Sandborn WJ, Assche G van, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257-265–3.
63. 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.
64. Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology 2012;143:1218-1226.
65. Travis SPL, Danese S, Kupcinskas L, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut 2014;63:433–441.
66. 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.
67. 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.
68. Prinsen CAC, Vohra S, Rose MR, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a "core outcome set." Trials 2014;15:247.
69. Hindryckx P, Baert F, Hart A, et al. Clinical Trials in Ulcerative Colitis: A Historical Perspective. J Crohns Colitis 2015;9:580–588.
70. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011;141:1194–1201.
71. Barreiro-de Acosta M, Vallejo N, Iglesia D de la, et al. Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 vs 1): A Longitudinal Cohort Study. J Crohns Colitis 2016;10:13–19.
72. Arai M, Naganuma M, Sugimoto S, et al. The Ulcerative Colitis Endoscopic Index of Severity is Useful to Predict Medium- to Long-Term Prognosis in Ulcerative Colitis Patients with Clinical Remission. J Crohns Colitis 2016;10:1303-1309.
73. Manginot C, Baumann C, Peyrin-Biroulet L. An endoscopic Mayo score of 0 is associated with a lower risk of colectomy than a score of 1 in ulcerative colitis. Gut 2015;64:1181–1182.
74. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol 2014;12:929–934.

Legends

Figure 1: Results after the first round of vote in the Delphi-style process for endoscopic definitions of remission in ulcerative colitis. Each of the 15 specialists ranked by importance from rank 1 (the most important) to rank 8 (the less important) each definition of remission among the 8 proposed at the first round of vote in the Delphi-like process. The figure displays the number of specialists who chose each rank for each of the four definitions with the lowest median ranks. These four definitions were those selected in the second round of vote. UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

Conflicts of interest

L Vuitton has received fees for lectures from Abbvie, Ferring, MSD, Hospira and Takeda.
P Marteau has received payments for lectures/speakers bureau participation from Abbvie, Ferring Pharmaceuticals, Hospira, Pfizer
JFC has served as a speaker for Abbvie, Ferring, Janssen, Merck & Co., Nutrition Science Partners Ltd., Takeda.
BP has received consulting fees from Abbvie, MSD, Pfizer, Biogaran and Vifor; and speaker fees from Abbvie, MSD, Ferring, Takeda, and Hospira.
GPdC has received lectures fees from Abbvie, MSD, Ferring, and consulting fees from Takeda.
AW has received consultancy speaking fees from Abbvie, Janssen Cilag, Ferring Pharmaceuticals, Orphan Australia and Shire, and sits on the following advisory boards: Abbvie, Ferring Pharmaceuticals, Takeda and Janssen Cilag.
S Travis : received consulting fees from AbbVie, Asahi-Kasei, Bristol-Myers Squibb, Coronado Biosciences, Cosmo Technologies Ltd., Ferring Pharmaceuticals, Genentech, Genzyme Corp., GlaxoSmithKline, Janssen, Lexicon Pharmaceuticals, Merck Research Laboratories, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceutical Co., Ltd., Novartis, Novo Nordisk A/S, NPS Pharmaceuticals, PDL BioPharma, Pfizer, Procter and Gamble, Santarus, Inc. (a wholly owned subsidiary of Salix Pharmaceuticals, Inc.), Schering Plough, Shire, Sigmoid Pharma Ltd., Tillotts Pharma AG, TxCell SA, UCB and Warner Chilcott UK Ltd.; he has received research grants from AbbVie, Genentech, GlaxoSmithKline, Janssen, Novartis, Pfizer, Procter and Gamble, Shire and UCB; and he has received payments for lectures/speakers bureau participation from AbbVie, Ferring Pharmaceuticals, Janssen and Warner Chilcott UK Ltd.
JY Mary : none
J Panés has received consulting fees from Abbvie, Boehringer Ingelheim, Ferring, Galapagos, Genentech-Roche, Janssen, Pfizer, Takeda, TiGenix and Topivert, and has received lecture fees from Abbvie, Janssen, MSD, and Pfizer.
Laurent Peyrin-Biroulet has received consulting fees from Abbott, BMS, Boehringer Ingelheim, Celltrion, Ferring, Genentech, Hospira, Janssen, Lilly, Merck, Mitsubishi, Norgine, Pharmacosmos, Pilège, Shire, Takeda, Therakos, Tillots, UCB and Vifor, and has received lecture fees from Abbott, Ferring, HAC-pharma, Janssen, Merck, Norgine, Therakos, Tillots and Vifor.

Contributorship statement

LV contributed to literature search, acquisition and interpretation of data and drafting of the manuscript. PM, JFC, BP, GPdC, AW, ST, JP contributed to literature search, expert panel for the Delphi like process and drafting of the technical review part.

JYM contributed to critical review of technical aspects, design of the voting process, analysis and interpretation of data. PM & LPB supervised the study.

All authors contributed to the critical revising and the final approval of the manuscript.

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Table 1: Endoscopic indices for ulcerative colitis: definitions, strengths and validation.

Name (year)	Endoscopic Items	Range	Validation yes/no	Reproducibility	Sensitivity to change	Practicability
Baron[3] (1964)	vascular pattern bleeding	**0-3**	**no**	moderate or poor	NA	+/-
Sutherland[5] UCDAI (1987)	friability bleeding ulcers	**0-3**	**no**	NA	NA	+/-
Feagan[6] "Modified Baron score" (2005)	granularity, friability, vascular pattern bleeding ulcers	**0-4**	**no**	moderate	small	+/-
Matts[11] (1961)	granularity, edema bleeding ulcers	**1-4**	**no**	moderate	inconclusive	-
Blackstone[12] (1984)	vascular pattern erythema bleeding ulcers, mucopus	**1-8**	**no**	moderate	NA	+/-
Rachmilewitz[13] (1989)	granularity vascular pattern bleeding ulcers, mucopus	**0-12**	**no**	NA	NA	+/-
Mayo sub-score[14] (1987)	erythema, friability vascular pattern bleeding ulcers	**0-3**	**no**	moderate	small	+
Osada[4] (2010)	erythema, friability, granularity, edema vascular pattern ulcers	**0-6**	**no**	moderate	NA	-
EAI[19] (2010)	edema, erythema bleeding mucopus ulcers	**0-16**	**no**	NA	inconclusive	-
UCCIS[20,21] (2013)	granularity vascular pattern bleeding/friability ulcers	**0-162**	**yes**	NA*	NA	-
UCEIS[9,22] (2012-2013)	vascular pattern bleeding erosions/ulcers	**0-8**	**yes**	moderate	moderate	+

EAI : Endoscopic Activity Index; NA : not available; UCCIS : Ulcerative Colitis Colonoscopic Index of Severity; UCDAI : Ulcerative Colitis Activity Index; UCEIS : Ulcerative colitis Endoscopic Index of Severity; * : for the UCCIS the reproducibility is available for each component but not for the index.

Table 3: Results of 1st and 2nd rounds of the vote by the 15 specialists for endoscopic definitions of remission and response in ulcerative colitis (UC). For the 1st vote, 8 definitions were retained for endoscopic remission, and 5 for endoscopic response. The 4 definitions with the highest median rank were selected and ordered by increasing median rank for the 2nd vote.

	1st Vote		2nd Vote			
	Median	Mean	Median	Mean	proportion of rank 1	proportion of rank 1 or 2
Definitions of endoscopic remission in UC						
UCEIS 0	2	2.4	1	1.60	0.67	0.80
Mayo endoscopic subscore 0	3	2.8	2	2.07	0.13	0.80
UCEIS ≤1	3	3.3	3	2.60	0.13	0.33
Mayo endoscopy subscore ≤1	4	3.6	4	3.73	0.07	0.07
Modified Mayo endoscopic score ≤1 and ≥1 point reduction	5.5	5.6				
Complete healing : no endoscopic lesion	6	5.1				
Normal mucosa, scarring or pseudo polyps	6	5.4				
Physician's assessment of endoscopic healing	8	7.9				
Definitions of endoscopic response in UC						
Decrease in Mayo endoscopic score ≥1 grade	2	2.1	2	2.07	0.47	0.60
Decrease in UCEIS ≥ 2 points	2	2.5	2	1.93	0.20	0.87
Decrease in UCEIS ≥ 2 point or UCEIS = 0	3	2.9	2	2.13	0.33	0.53
Decrease in UCEIS ≥ 1 point	3	3.2	4	3.87	0	0
Any improvement	5	4.8				

The four last definitions of endoscopic remission and the last one of endoscopic response were not part of the second vote due to their poor performance at the first vote according to the 15 specialists.
UC: Ulcerative Colitis; UCEIS: Ulcerative Colitis Endoscopic Index of Severity

Table 2: Definitions of endoscopic remission and endoscopic response in ulcerative colitis trials.

Author	Year	Drug	Definition of endoscopic remission	Definition of endoscopic response	Outcome	Trial
Truelove SC[2]	1955	prednisone	ND	Physician assessment of endoscopic improvement	6 weeks	OL
Jewel DP[28]	1974	azathioprine	ND	Decrease in endoscopic score ≥1 grade (0=normal;1=mild;2=moderate;3=severe)	4 weeks	RCT
Kam L[29]	1996	mesalazine enema *vs* sulfasalazine	Mayo endoscopic score 0	ND	6 weeks	RCT
Löfberg R[30]	1996	budesonide *vs* prednisone	Score 0 (4 grade scale 0-3)	ND	9 weeks	RCT
Lee FI[31]	1996	mesalazine *vs* prednisone enema	Achievement of grade 1 in a Sigmoidoscopic score	ND	4 weeks	RCT
Kruis W[32]	1998	olsalazine *vs* mesalazine	Score 0 or 1 (5 point scale derived from Rachmilewitz')	ND	12 weeks	RCT
Vernia P[33]	2000	mesalazine	ND	Reduction of the UCDAI score ≥2	6 weeks	RCT
Vecchi M[34]	2001	mesalazine	Rachmilewitz < 4	ND	6 weeks	RCT
D'Haens[35]	2001	cyclosporine *vs* corticosteroids	ND	Decrease in endoscopic score ≥1 grade	Day 8	RCT
Green JR[36]	2002	balsalazide *vs* sulfasalazine	Baron score ≤1	ND	12 weeks	RCT
Mansfield JC[37]	2002	balsalazide *vs* sulfasalazine	Normal rectal mucosa or minimal erythema	ND	8 weeks	RCT
Levine DS[38]	2002	balsalazide *vs* mesalazine	Unique endoscopic score: Normal or mild	ND	8 weeks	RCT
Pruitt R[39]	2002	balsalazide *vs* mesalazine	Unique endoscopic score: Normal or mild	ND	8 weeks	RCT
Rizzello F[40]	2002	beclomethasone dipropionate	Baron score: normalization	ND	4 weeks	RCT
Campieri M[41]	2003	beclometasone dip. *vs* mesalazine	ND	Baron score-significant improvement	4 weeks	RCT
Raedler A[42]	2004	mesalazine	Rachmilewitz ≤ 2	ND	8 weeks	RCT
Hanauer SB[43]	2005	mesalazine	Normal endoscopic finding	ND	6 weeks	RCT
Marakhouski Y[44]	2005	mesalazine	Rachmilewitz < 4	ND	8 weeks	RCT

Järnerot G [45]	2005	infliximab	ND	improvement (ND)	4 weeks	RCT
Rutgeerts P[46]	2005	infliximab	Mayo endoscopic score ≤1	ND	weeks 8, 30, 54	RCT
Gibson PR[47]	2006	mesalazine	Rachmilewitz <4	Decrease in Rachmilewitz ≥1 point	8 weeks	RCT
D'haens G[48]	2006	mesalazine MMX	Mayo endoscopic score ≤1	ND	8 weeks	RCT
Ardizzone S[49]	2006	azathioprine *vs* mesalazine	Baron score ≤1	ND	3-6 months	RCT
Hanauer SB[50]	2007	mesalazine	Normal endoscopic finding	Improvement in endoscopic findings	6 weeks	RCT
Lichtenstein GR[12]	2007	mesalazine MMX	mMayo endoscopic score ≤1	ND	8 weeks	RCT
Kamm MA[51]	2008	mesalazine MMX	mUCDAI endoscopic score ≤1	ND	8 weeks	RCT
Cortot A[52]	2008	mesalazine foam	Rachmilewitz < 4	ND	4 weeks	RCT
Kruis W[53]	2009	mesalazine	Rachmilewitz < 4, modified Mayo ≤ 1	ND	8 weeks	RCT
Scherl EJ[54]	2009	mesalazine	mMayo endoscopic score ≤ 1	Decrease in Mayo endoscopic score ≥1 point	8 weeks	RCT
Barreiro dA M[55]	2009	infliximab	Mayo endoscopic score ≤1	ND	104 weeks	OL
Afif W[56]	2009	adalimumab	Mayo endoscopic score ≤1	ND	8 weeks	OL
Reinisch W[57]	2011	adalimumab	Mayo endoscopic score ≤1	ND	8 weeks	RCT
Gong Y[58]	2012	Fufangkushen *vs* mesalazine	Mayo endoscopic score ≤1	ND	8 weeks	RCT
Ogata H[59]	2012	tacrolimus	Mayo endoscopic score ≤1	ND	2 weeks	RCT
Laharie D[60]	2012	cyclosporine vs infliximab	Mayo endoscopic score ≤1	ND	14 weeks	RCT
Sandborn WJ[61]	2012	tofacitinb	Mayo endoscopic score 0	Decrease in Mayo endoscopic score ≥1 point	8 weeks	RCT
Sandborn WJ[62]	2012	adalimumab	Mayo endoscopic score ≤1	ND	8-52 weeks	RCT
Feagan B[63]	2013	vedolizumab	Mayo endoscopic score ≤1	ND	6 weeks	RCT

Sandborn WJ[64]	2012	budesonide MMX	mUCDAI endoscopic score ≤1 , and ≥1 point reduction in endoscopy score	Decrease in UCDAI endoscopic score ≥1 grade	8 weeks	RCT
Travis SP[65]	2014	budesonide MMX	mUCDAI endoscopic score ≤1, and ≥1 point reduction in endoscopy score	Decrease in UCDAI endoscopic score ≥1 grade	8 weeks	RCT
Panaccione R[66]	2014	infliximab + azathioprine	Mayo endoscopic score ≤1	ND	16 weeks	RCT
Sandborn WJ[67]	2014	golimumab	Mayo endoscopic score ≤1	ND	6 weeks	RCT

UCDAI= Ulcerative Colitis Disease Activity Index (also called Sutherland index); mMayo = modified Mayo and mUCDAI = modified UCDAI : mucosal friability was given a score of 2 rather than 1; OL = Open Label ; MMX=multi-matrix system; RCT = randomized controlled trial.