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SPECIAL REPORTS AND REVIEWS

A Review of Activity Indices and Efficacy End Points for Clinical Trials of Medical Therapy in Adults With Ulcerative Colitis

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See Sparrow MP et al on page 209 and Yacyshyn B et al on page 215 in the February 2007 issue of *CGH*.

Ulcerative colitis (UC) is a common gastrointestinal disorder in adults. Recent advances in pathophysiology, immunology, and pharmaceutical science have resulted in a large number of medications including biologic agents with potential application to the treatment of UC. Clinical development of these drugs requires well-controlled trials evaluating safety and efficacy. The first randomized controlled trial in UC dates back to 1955 when cortisone was shown to be effective for the treatment of active disease. Further experience in clinical trial design for UC during the last 50 years has led to the creation of a large number of disease-specific measures of disease activity. Natural history studies have allowed the classification of UC patients into subpopulations based on anatomic extent of disease, severity of disease, and prolonged treatment with corticosteroid therapy. Currently, important differences exist among investigators and regulatory agencies in the use of measures of response. This article presents the consensus of an international group of specialists on classification, treatment indications, and clinical trial efficacy end points for the medical therapy of UC.

The Consensus Process

The need for a systematic evaluation of the outcomes used for clinical trials in UC came about from perceived inconsistencies in regulatory decision making. This issue was identified by a few individuals who are regularly involved in the design and implementation of randomized controlled trials of therapy for this disorder. The clinical trials task force of the International Organization of Inflammatory Bowel Disease (IOIBD) initiated this process of developing a systematic review in 2003. Studies were selected for inclusion if they (1) first described a measurement instrument, (2) modified or validated an existing instrument, or (3) provided an illustrative example of the use of a measurement in a clinical trial (in some instances for regulatory approval). The task force met initially in person for discussion. The results were summarized in a draft manuscript by the primary authors (G.D. and W.J.S.) and discussed at the annual IOIBD meetings in 2004 and 2005. The manuscript was then circulated to the entire IOIBD membership; the leadership of the European Crohn's and Colitis Organization (ECCO); the leadership of 3 groups of investigators who conduct clinical trials in inflammatory bowel disease (IBD) in the United States (the clinical alliance of the Crohn's and Colitis Foundation of America), Canada (the clinical network of the Crohn's and Colitis Foundation of Canada), and France (the Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives); and to pharmaceutical companies who conduct clinical trials in UC including Abbott Laboratories, Ardeypharm, Asahi Kasei Medical, AstraZeneca, Axcan Pharma, Centocor, Elan, Dr. Falk Pharma, Ferring Pharmaceuticals, Giuliani SPA, Otsuka Pharmaceuticals, Proctor & Gamble Pharmaceuticals, Protein Design Labs, Salix Pharmaceuticals, Shire Pharmaceuticals, Schering AG, Schering Plough Corporation, and UCB. The manuscript was again extensively edited and revised and then discussed by the entire IOIBD membership at the annual general meeting in 2006. Following that meeting, additional revisions were made, and the review was submitted for publication. External peer review by the journal *Gastroenterology* led to a final revision that is presented below.

Consensus statements can be classified with respect to the strength of the evidence supporting the conclusions (level 1, randomized controlled trials; level 2, well-designed cohort and case control studies; level 3, expert opinion based on observational data).[1] There have been no randomized controlled trials or subexperimental studies that have compared the utility of the different mea-

Abbreviation used in this paper: ESR, erythrocyte sedimentation rate.

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sures of outcome for determining the disease activity of UC, and virtually none of the instruments discussed below have been validated (defined as the extent to which a scale measures what it is intended to measure).[2] No formal quantitative process was used to reach the conclusions outlined below. Rather, the authors reviewed the relevant medical literature and considered factors such as clinical relevance, use in multiple clinical trials, use in clinical trials that lead to regulatory approval, and others in forming an expert opinion. Thus, the evidence summarized in this review is all level 3.

Instruments for Measuring Disease Activity in UC

Definitions

The scores described below are based on signs and symptoms for which no standard definitions have been developed. A "bowel movement" for instance could be any trip to the bathroom with passage of fecal material through the anus, but some patients with severe disease may be incontinent making the definition unsuitable.[3] The upper limit of normal for stool frequency is quite variable and may be up to 3 or 4 stools per day. Thus, defining an increased stool frequency may require a comparison to a patient's "normal" stool frequency, which could be preferable to setting an absolute number of stools per day. On the other hand, the "normal" number of bowel movements for any individual patient can also vary considerably. The same is true for "fecal urgency" and "abdominal pain," often interpreted as combined cramps and dull discomfort. The authors recommend that, in the future, more stringent definitions be discussed and developed.

Instruments for Measuring Disease Activity Based on Clinical and Biochemical Disease Activity

Truelove and Witts Severity Index. In 1955, Truelove and Witts reported the results of a placebo-controlled trial of oral cortisone for treating active UC. The authors described an instrument to measure disease activity subsequently named the Truelove and Witts Severity Index,[4] composed of 6 variables: number of stools per day; blood in stools; temperature; pulse; hemoglobin; and erythrocyte sedimentation rate (ESR) (see Supplementary Table 1 online at www.gastrojournal.org). Clinical remission was defined as 1 or 2 stools per day without blood, absence of fever or tachycardia, a normal hemoglobin or "returning towards normal," a normal ESR or "returning towards normal," and gaining weight. To be included in this category, patients were expected to show all of the above features. No change or worse was described as "self-explanatory." All intermediate cases were defined as "improved."

This instrument has multiple limitations. Most notably, neither the Truelove and Witts Severity Index nor the definitions of "clinical remission," "improvement," and "no change" or "worsening" have been validated, and it is not quantitative, ie, no disease severity score is generated. Although the Truelove and Witts Severity Index is useful to broadly classify patients and therefore can be used as an entry or exclusion criteria for clinical trials, it is not sufficiently discriminative to measure changes in disease activity.[4]

Powell-Tuck Index (also known as the St. Mark's Index). In 1978, Powell-Tuck et al reported the results of a controlled comparison of oral prednisolone 10 mg 4 times daily vs 40 mg once daily for the treatment of active UC. The authors described a disease activity measure subsequently named the Powell-Tuck Index,[5] including 10 clinical variables: general health, abdominal pain, bowel frequency, stool consistency, bleeding, anorexia, nausea or vomiting, abdominal tenderness, extraintestinal complications (eye, mouth, joint, skin), and temperature (see Supplementary Table 2 online at www.gastrojournal.org). The scores range from 0 to 20 points. One variation of the Powell-Tuck Index includes sigmoidoscopic appearance (0–2 points), increasing the total maximum score to 22 points (see Supplementary Table 2 online at www.gastrojournal.org). Remission was defined as a score of 0, and improvement was defined as a decrease in the baseline score $\geq$2 points. Neither the Powell-Tuck Index nor the definitions of remission and improvement have been validated. Each of the 10 clinical variables was correlated with the sigmoidoscopic appearance in a patients' cohort.[6] Rectal bleeding, abdominal pain, bowel frequency, stool consistency, and well-being correlated best with endoscopic changes. The sigmoidoscopic appearance contributes little to the variance of the Powell-Tuck Index score[7] because only 2 points of the maximum 22 points come from sigmoidoscopy. The 7 patient self-reported items (general health, abdominal pain, bowel frequency, stool consistency, bleeding, anorexia, nausea or vomiting) correlate well with the total index score.[8] A cut-off of $<$3.5 points correlates with Patient-Defined Remission (see below).[9]

Clinical Activity Index (also known as the Rachmilewitz Index). In 1988, Rachmilewitz et al reported the results of a controlled comparison of coated mesalamine (Claversal; Smith Kline Beecham, United Kingdom) and sulfasalazine for the treatment of active UC. In this trial, the authors described an instrument subsequently named the Clinical Activity Index (CAI)[10] composed of 7 variables: number of stools, blood in stools, investigator's global assessment of symptomatic state, abdominal pain or cramps, temperature due to colitis, extraintestinal manifestations, and laboratory findings (see Supplementary Table 3 online at www.gastrojournal.org). The scores ranging from 0 to 29 points (higher scores meaning more severe disease) have been validated in one study[11] in which clinical remission was defined as a CAI score $\leq$4 points.

Activity Index (also known as the Seo Index). In 1992, Seo described an activity index (AI)[12] based on evaluation of 18 clinical, laboratory, and endoscopic variables that were prospectively collected from 72 patients during 85 clinical relapses. A multivariable regression analysis was used to develop an equation that best predicted the Truelove and Witt's Severity Index classification (mild, moderate, severe) for each patient. Five variables were defined: bloody stool, bowel movements, ESR, hemoglobin, and serum albumin. The AI is calculated as follows: AI = 60 × bloody stool + 13 × bowel movements + 0.5 × ESR − 4 × hemoglobin − 15 × albumin + 200. Scores range from approximately 50 to 250 points. Activity index scores <150 points, 150–200 points, and >200 points correspond to mild, moderate, and severely active disease, respectively, as classified by the Truelove and Witts Severity Index. In a subsequent study performed in patients with severe UC, an AI score <180 points after 2 weeks of intravenous corticosteroids predicted remission. Conversely, a score >200 predicted colectomy.[13,14] The AI significantly predicted response to infliximab or need for colectomy in a clinical trial.[15] The AI also correlates significantly with endoscopic findings.[16] A cut-off of <120 points correlates with Patient-Defined Remission (see below).[9] A decrease of >30 points from baseline correlates with Patient-Defined Significant Improvement (see below).[9]

Physician Global Assessment. In 1993, Hanauer et al reported the results of a placebo-controlled trial of sustained release mesalamine (Pentasa; Ferring, Copenhagen, Denmark, and Shire, Basingstoke, United Kingdom) for the treatment of active UC. In this trial, the authors utilized a Physician Global Assessment (PGA).[17] The PGA is an arbitrarily designed, multicomponent measure of disease activity that uses the physician's assessment of improvement or worsening in clinical status based on disease activity and symptom severity as compared with baseline (see Supplementary Table 4 online at www.gastrojournal.org). Scores range from 1 to 6 points, with higher scores meaning more severe disease, and treatment success was defined as a PGA score of 1 or 2, whereas treatment benefit was defined as any improvement of PGA score over baseline and remission as a PGA score of 1. The PGA and the definitions of treatment success, benefit, or remission have not been validated.

Lichtiger Index (also known as the Modified Truelove and Witts Severity Index). In 1990, Lichtiger et al reported the results of a pilot trial of intravenous cyclosporine for the treatment of severely active steroid-refractory UC. In this trial, the authors described a modified Truelove and Witts Severity Index (MTWSI), also referred to as the Lichtiger Index.[18] Eight variables determine the Lichtiger Index: diarrhea (number of daily stools), nocturnal stools, visible blood in stool (percentage of movements), fecal incontinence, abdominal pain/cramping, general well-being, abdominal tenderness, and need for antidiarrheals (see Supplementary Table 5 online at www.gastrojournal.org). The scores range from 0 to 21 points. Clinical response was initially defined as a score reduction from baseline of ≥50%.[18] Subsequently, clinical response was defined as a Lichtiger Index score <10 points on 2 consecutive days.[19] Recently, remission was defined as a Lichtiger Index score ≤3.[20] Neither the Lichtiger Index nor the definitions of clinical response or remission have been validated.

Investigators Global Evaluation. In 1998, Hanauer et al reported a placebo-controlled trial of budesonide enemas for active distal UC in which they described a disease activity measure subsequently named the Investigators Global Evaluation.[21] The Investigators Global Evaluation is an arbitrarily designed, multicomponent measure using the physician's assessment of disease severity based on disease activity and symptom severity compared with baseline (see Supplementary Table 6 online at www.gastrojournal.org). The scores range from 0 to 4 points, with remission defined as ≤3 bowel movements per day, no blood in stools, no urgency, no abdominal pain or painful evacuations, and a sigmoidoscopic inflammation grade of 0. Neither the Investigators Global Evaluation nor the definition of remission has been validated.

Simple Clinical Colitis Activity Index. In 1998, Walmsley et al described an instrument to measure disease activity named the Simple Clinical Colitis Activity Index (SCCAI).[22] Investigators adapted the 10 items of the Powell-Tuck Index and added 3 additional items: sigmoidoscopic assessment,[5] nocturnal bowel movements, and urgency of defecation. Furthermore, the general well-being score from the Harvey and Bradshaw index of Crohn's disease was substituted for the general health question of the Powell-Tuck Index.[23] In the study that evaluated 57 patients during 63 assessments, multivariable regression analysis was used to develop an equation that contained 6 variables that best predicted the Powell-Tuck Index classification: bowel frequency (day), bowel frequency (night), urgency of defecation, blood in stool, general well-being, and extracolonic manifestations (see Supplementary Table 7 online at www.gastrojournal.org). Scores range from 0 to 19 points. Although clinical remission and response criteria were not defined in the original study, a cut-off of <2.5 points has been shown to correlate with Patient-Defined Remission,[9] and a decrease of >1.5 points from baseline correlates with Patient-Defined Significant Improvement (see below).[9]

Improvement Based On Individual Symptom Scores. In 2002, Levine et al reported the results of a controlled trial of balsalazide for the treatment of active UC. In this trial, the authors described an instrument to measure disease improvement based on individual symptom scores[24] including rectal bleeding, patient functional assessment, stool frequency, abdominal pain, sigmoidoscopic grade, and PGA (see Supplementary Table 8 online at www.gastrojournal.org). The scores for each item range

from 0 to 3 points (normal to severe). Improvement was defined as a reduction from baseline of ≥1 grade in rectal bleeding and at least one of the other assessed symptoms. Improvement based on individual symptom scores has not been validated as a measure of disease activity.

Ulcerative Colitis Clinical Score. In 2005, Feagan et al reported the results of a placebo-controlled trial of anti-$\alpha 4\beta 7$ integrin antibody (MLN-02) for the treatment of active UC. In this trial, the Ulcerative Colitis Clinical Score (UCCS) was described.[25] This instrument consists of 4 items: stool frequency, rectal bleeding, subject's (patient's) functional assessment, and PGA (see Supplementary Table 9 online at www.gastrojournal.org). This instrument is a modification of the Mayo Score (see below).[26] Scores range from 0 to 12 points with higher scores meaning more active disease. Clinical remission was defined as a UCCS score of 0 or 1 and a modified endoscopic Baron score of 0 or 1 (see below) and no rectal bleeding. Clinical response was defined as an improvement of 3 points or more on the UCCS. Neither the UCCS nor the definitions of clinical remission or clinical response have been validated.

Patient-defined remission. In 2005, Higgins et al described an index named Patient-Defined Remission.[9] Investigators asked 56 patients the survey question, "Is your ulcerative colitis in remission (not active)?" to which only yes or no answers were accepted. At a return visit between 1 and 14 months later, subjects were again asked whether they were in remission and whether their UC was better or worse than at their previous visit on a 7-point Likert scale (1, much better; 2, some better; 3, a little better; 4, about the same; 5, a little worse; 6, some worse; 7, much worse). Subjects who reported being either much better or some better were defined as significantly improved. Those who were a little better, about the same, or one of the 3 levels of worsening were not considered significantly improved. Patient-Defined Remission had good sensitivity (86%) and specificity (76%) for a "regulatory definition of remission" defined by investigators as a composite of a modified Baron endoscopic score graded 0–2 (absence of friability) and absence of visible blood reported by the patient.

Instruments for Measuring Disease Activity Based on Endoscopic Disease Activity

Truelove and Witts Sigmoidoscopic Assessment. Truelove and Witts performed serial sigmoidoscopic assessments during a placebo-controlled trial of cortisone for the treatment of active UC. Sigmoidoscopic appearance was classified as (1) normal or near normal (defined as slight hyperemia or only slight granularity), (2) improved, or (3) no change or worse.[4] The absence of definitions for the endoscopic descriptors may create interobserver variability.

Baron score. In a cross-sectional study, Baron et al specifically evaluated the interobserver variability in describing the appearance of the rectosigmoid mucosa using a rigid proctoscope in patients with UC. The endoscopic disease activity was rated using a 4-point scale (0–3) (see Supplementary Table 10 online at www.gastrojournal.org)[27] that was mainly based on the severity of bleeding. Notably, ulceration was not assessed. Interobserver variation was calculated for all variables and was the highest for "graded" variables such as "redness." However, the best agreement was reached for "friability" (bleeding to light touch).

Powell-Tuck Sigmoidoscopic Assessment. Powell-Tuck et al performed serial sigmoidoscopic assessments during a controlled trial of oral prednisolone for the treatment of active UC. The sigmoidoscopic appearance was described using a 3-point scale (0–2), again with focus on "bleeding" as a predominant endoscopic feature (see Supplementary Table 2 online at www.gastrojournal.org).[5]

Endoscopic Index (also known as the Rachmilewitz Endoscopic Index). Rachmilewitz performed serial endoscopic assessments during a controlled comparison of coated mesalamine and sulfasalazine for the treatment of active UC. In this trial, an instrument consisting of 4 items was described: granulation scattering reflected light, vascular pattern, vulnerability of mucosa, and mucosal damage (mucus, fibrin, exudates, erosions, and ulcer) (see Supplementary Table 11 online at www.gastrojournal.org).[10] Scores range from 0 to 12 points. Endoscopic remission was defined as an endoscopic index score of 0–4 points. The instrument has not been validated.

Sigmoidoscopic Index. Hanauer et al performed serial endoscopic assessments during a placebo-controlled trial of sustained release mesalamine (Pentasa; Ferring and Shire) for the treatment of active UC. They described the Sigmoidoscopic Index.[17] Its 5 variables were erythema, friability, granularity/ulceration, mucopus, and disappearance of mucosal vascular pattern. Each variable was assigned a value from 0 to 3 (0, normal; 1, mild; 2, moderate; 3, severe). The total scores for the Sigmoidoscopic Index range from 0 to 16 points. Sigmoidoscopic remission was defined as a Sigmoidoscopic Index score of 0 to 4 points, which has not been validated.

Sigmoidoscopic Inflammation Grade Score. Lémann et al[28] and later Hanauer et al[21] performed serial endoscopic assessments during a comparative trial with budesonide and 5-ASA enemas and during a placebo-controlled trial of budesonide enemas for the treatment of active distal UC. The authors described the Sigmoidoscopic Inflammation Grade Score,[21,28] which was a 4-point scale (0–3): 0, normal mucosa; 1, edema and/or loss of visible mucosal vascularity, granularity; 2, friability (defined as visible, induced bleeding on examination), petechiae; and 3, spontaneous hemorrhage, visible ulcers. No definition of improvement in sigmoidoscopic inflammation was identified.

Mayo Score Flexible Proctosigmoidoscopy Assessment. Schroeder et al performed serial flexible proctosigmoidoscopic assessments during a placebo-controlled trial of oral delayed release mesalamine (Asacol; Procter & Gamble, Cincinnati, OH) for treatment of active UC. The appearance of the rectal mucosa was described using a 4-point scale (0–3) (see Supplementary Table 13 online at www.gastrojournal.org).[26] In 2 studies of infliximab therapy for active UC, mucosal healing was defined as a subscore of 0 or 1 among patients with a baseline score of 2 or 3.[29] This definition of endoscopic improvement in flexible proctosigmoidoscopic assessment (mucosal healing) has not been validated.

Sutherland Mucosal Appearance Assessment. Sutherland et al performed serial sigmoidoscopic assessments during a placebo-controlled trial of mesalamine enemas (Rowasa enemas; Solvay, Brussels, Belgium) for the treatment of active distal UC. The sigmoidoscopic appearance was described on a 4-point scale (0–3) (see Supplementary Table 14 online at www.gastrojournal.org),[30] but no further validation was performed.

Modified Baron Score. Feagan et al performed serial endoscopic assessments during a placebo-controlled trial of anti-$\alpha 4\beta 7$ integrin antibody (MLN-02) for active UC, describing endoscopic activity on a 5-point scale (0–4) (see Supplementary Table 12 online at www.gastrojournal.org). With this modified Baron Score (see above),[27] endoscopic remission was defined as a Modified Baron Score of 0. Endoscopic response was defined as an improvement of the Modified Baron Score of at least 2 grades from baseline. Neither the Modified Baron Score nor the definitions of endoscopic remission or endoscopic response have been validated.

Instruments for Measuring Disease Activity: Composite Clinical and Endoscopic Disease Activity Indices

Several disease activity indices incorporate both clinical and endoscopic parameters into a composite index. A recent study looked at the value of adding endoscopic evaluations to clinical scores in 66 patients with active UC and concluded that 2 indices *not* using endoscopy ("noninvasive indices": the simple colitis clinical activity index [SCCAI] and activity index [AI or Seo index]) correlated well with the "invasive" (including endoscopy subscore) Powell-Tuck Index and Sutherland Index (UC disease activity index).[7] The Sutherland Index endoscopy subscore predicted only 0.04% of the variance in the Powell-Tuck Index. The authors concluded that endoscopy contributes little to indices of UC disease activity. However, it should be emphasized that the endoscopic subscore accounts for only 2 of 22 points in the Powell-Tuck (St. Marks) Index and 3 of 12 points in the Sutherland Index.

Mayo Score (also known as the Mayo Clinic Score and the Disease Activity Index). In 1987, Schroeder et al reported the results of a placebo-controlled trial of oral delayed release mesalamine (Asacol) for the treatment of active UC. In this trial, the authors described an instrument to measure disease activity subsequently named the Mayo Score (also commonly referred to as the Mayo Clinic Score or the Disease Activity Index [DAI])[26] that consists of 4 items: stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy, and PGA (see Supplementary Table 13 online at www.gastrojournal.org). Scores range from 0 to 12 points. In addition to these items, a patient's functional assessment is also measured that is not meant to be included in the 12-point index calculation but should be used as a measure of general well-being when determining the PGA score. Complete response (remission) is defined as complete resolution of (1) stool frequency (normal stool frequency), (2) rectal bleeding (no rectal bleeding), (3) patient's functional assessment score (generally well), (4) endoscopy findings (normal), AND a PGA score of 0.[26,31,32] Partial response requires improvement (a minimum 1-point decrease from baseline) in the PGA score AND improvement in at least one other clinical assessment (stool frequency, rectal bleeding, patient's functional assessment, endoscopy findings) AND no worsening in any other clinical assessment. Neither the Mayo Score nor the definitions of complete response or partial response have been validated.[26,31,32]

Subsequent studies have modified the Mayo Score and/or these definitions. In a study of cyclosporine enemas for active left-sided UC, clinical remission was defined as a Mayo Score of 0 and clinical improvement as a decrease from baseline in the Mayo Score $\geq$3 points.[33] In a study of transdermal nicotine for active UC, clinical remission was defined as a Mayo Score of 0 and clinical improvement as a decrease from baseline in the Mayo Score $\geq$3 points (or a decrease of $\geq$2 points if the baseline Mayo Score was $\leq$3 points).[34] In studies of repifermin and daclizumab for active UC, remission required subscores of 0 for both sigmoidoscopy and rectal bleeding and a score of 0 or 1 for stool frequency and PGA subscores. Response was a decrease from baseline in the Mayo Score $\geq$3 points; clinical response was a decrease from baseline in the Mayo Score (without the endoscopy subscore, also know as a Partial Mayo Score) $\geq$2 points, and endoscopic response was a decrease from baseline in the endoscopic subscore $\geq$1 point.[35,36] In 2 studies of infliximab for active UC, clinical remission was defined as a total Mayo score of $\leq$2 points with no individual subscore $>$1 point, clinical response was a decrease from baseline in the total Mayo score $\geq$3 points and $\geq$30% and a decrease in the rectal bleeding subscore $\geq$1 point or an absolute rectal bleeding subscore of 0 or 1, and mucosal healing was defined as an absolute endoscopy subscore of 0 or 1.[29] Although the Mayo Score

has not been formally validated, the clinical relevance of these definitions used in the infliximab trials was demonstrated by showing that both definitions correlated with significant improvement in disease-specific health-related quality of life as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ)[37] and in generic quality of life as measured by the Short Form-36 (SF-36) questionnaire.[38–40]

Sutherland Index (also known as the Disease Activity Index and the UC Disease Activity Index). In 1987, Sutherland et al reported the results of a placebo-controlled trial of mesalamine enemas (Rowasa enemas; Solvay, Belgium) for the treatment of active distal UC.[30] In this trial, the authors described the Sutherland Index (also known as the Disease Activity Index [DAI] and the UC Disease Activity Index [UCDAI]).[30] Four variables determine the Sutherland Index: stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity (see Supplementary Table 14 online at www.gastrojournal.org). Scores range from 0 to 12 points. In this trial, efficacy was defined as a statistically significant reduction in the Sutherland Index score (percentage change from baseline calculated by taking the average of the percentage change from baseline for each individual patient) and a significant reduction in the individual subscores (calculated by taking the average of the absolute change from baseline for each individual patient).[30] In 2 studies of oral mesalamine for active UC, remission was defined as Sutherland score of $\leq$1 point with a score of 0 for rectal bleeding and stool frequency, and $\geq$1-point reduction from baseline in sigmoidoscopy score and friability (within the sigmoidoscopy score) was moved from a score of 1 to 2 thereby making the definition of remission more stringent.[41,42] Clinical improvement was defined as a reduction in the Sutherland score $\geq$3 points from baseline.[41,42] Although the Sutherland Index has not been formally validated, a score of $<$2.5 points has been shown to correlate with Patient-Defined Remission (see above).[9]

Instruments for Measuring Quality of Life

Disease-specific quality-of-life instruments for patients with UC include the Rating Form of IBD Patient Concerns[43–50] and the Inflammatory Bowel Disease Questionnaire (IBDQ).[37,51–53] The IBDQ is a 32-item questionnaire with 4 dimensions (bowel function, emotional function, systemic symptoms, social function); the total score on this index ranges from 32 to 224, with higher scores indicating better quality of life. The scores of patients in remission usually range from 170 to 190.[37] The IBDQ can be self-administered,[54] and a shortened 10-question version has been validated.[55] The IBDQ has been used as a secondary end point in relatively few clinical trials in patients with UC,[25,29,40] but it has been used and validated extensively for Crohn's disease.

Instruments for Measuring Histologic Disease Activity

Given that the rectum is usually involved, the inflammation is generally mucosal and diffuse, and the rectal mucosa is accessible for histologic sampling, rectal biopsy is a potentially useful means of evaluating disease severity.[56] Rectal biopsy has also been used for judging therapeutic efficacy since 1966.[57] Features for consideration include the presence of polymorphonuclear leukocytes, the formation of crypt abscesses and ulceration, and the intensity of the mononuclear cell infiltrate in the lamina propria as well as structural abnormalities of the crypts and surface. Active disease is defined by the presence of neutrophils in conjunction with epithelial cell damage.[58] Inactive chronic disease permits the presence of architectural changes (irregular surface and crypt abnormalities) and an increase of lamina propria mononuclear cells Quiescent disease means the presence of architectural changes without alterations in the intensity and composition of the lamina propria cellular infiltrate.[59] Several scores for the assessment of histologic disease activity have been developed.[6,17,21,24,60–64] Mucosal inflammation is usually graded by means of a scale composed of different features selected because they have proved sensitive in characterizing the process.[63,65] Analysis generally relies on the examination of H&E-stained sections of 1 single biopsy. Two samples are suggested as more appropriate because it is well-known now that treatment may induce a variably intense inflammation.[66] Up to 6 samples have been studied, but the optimal number of necessary sections to be examined has not been determined. The reproducibility of the histologic activity scores has not been studied extensively, but limited data available show good agreement between different observers for the scores that have been evaluated.[63,64] Correlations between histologic disease activity and other assessments of disease activity are fair. In general, a good correlation is found between endoscopy and histology, especially when the samples are obtained during active inflammation. However, microscopic features of activity may persist in macroscopically inactive disease.[6,56,60,64,67] The correlation between the clinical indices of activity and histology is variable. A poor correlation was found between histologic findings and indices of activity for UC in some older studies.[67] At present, no single histology score is considered optimum, but it is generally recommended to include histology as a secondary end point for the assessment of the therapeutic efficacy. The Geboes Index has been validated and tested for reproducibility[64] and has 6 domains: structural (architectural) change, chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction, and erosions or ulceration (see Supplementary Table 15 online at www.gastrojournal.org). Scores range from 0 to 5.4, with higher scores indicating more severe histologic inflammation. The Geboes Index has

been used as a secondary end point in relatively few clinical trials in UC.[68,69] The Riley Index is also composed of 6 domains: the acute inflammatory cell infiltrate (polymorphonuclear cells in the lamina propria), the chronic inflammatory cell infiltrate (round cells in the lamina propria), crypt abscesses, mucin depletion, surface epithelial integrity, and crypt architectural irregularities (see Supplementary Table 15 online at www.gastrojournal.org).[62] Each feature is graded on a 4-point scale corresponding to none, mild, moderate, or severe. The final grade is the mean of 2 independent assessments. The Riley Index was assessed for interobserver variability in the original publication and in a cohort of Australian patients and found to be highly reproducible.[62,70] It has also been used in relatively few clinical trials.[25,70,71] The differences between the Geboes Index and the Riley Index are the stepwise assessment and a more elaborate grading of crypt lesions and surface epithelial damage in the Geboes Index.

Definitions of Patient Subpopulations

Classification and Treatment Indications According to Disease Extent

Colonoscopy can be used to classify patients with UC according to the macroscopic extent of disease. Population-based studies from Scandinavia have demonstrated that, at diagnosis, 40% of patients with UC have disease limited to the rectum (ulcerative proctitis), 30%–40% to the rectosigmoid colon (ulcerative proctosigmoiditis) or the left-colon (left-sided UC), and 20%–30% have disease extending proximal to the splenic flexure or involving the entire colon (extensive UC or substantial UC and pancolonic or universal UC).[72,73] Patients with ulcerative proctitis and ulcerative proctosigmoiditis are collectively termed *distal UC*. This anatomic classification has implications for prognosis because patients with extensive UC have higher rates of colectomy,[74] colorectal dysplasia, and cancer.[75] Anatomic classification is also useful for selecting appropriate patients for treatment with targeted delivery systems: suppositories can only be expected to release medication in the rectum (approximately the last 15 cm of the colon)[76,77]; liquid enemas will reach the descending colon/splenic flexure in approximately 80%–90% of patients.[78,79] It should be noted that approximately 50% of patients with left-sided UC at diagnosis will subsequently experience proximal extension of the inflammation during follow-up.[80] Previous studies have categorized patients as ulcerative proctitis, left-sided UC, pancolonic UC. Recently, the concept of UC as a "continuous disease" has been questioned, based on a large series of observational studies in which patients with left-sided UC had right-sided disease in the periappendiceal area to as distal as the hepatic flexure.[81] Some patients with UC may have "rectal sparing."[82] The prevalence of these variants has not been established in rigorous epidemiologic studies. Importantly, medical therapy can also induce patchy improvement of mucosal lesions.[83]

Classification and Treatment Indications According to Disease Activity

Patients with UC have a spectrum of disease severity ranging from remission to severely active. Clinical assessment can be used to classify UC patients into 4 disease activity subgroups: (1) remission (≤2 or 3 stools/day, without the presence of blood and/or pus in the stools, with no systemic symptoms); (2) mildly active disease (3 or 4 stools/day and/or presence of blood and/or pus in the stools less than daily, with no systemic symptoms of fever or weight loss); (3) moderately active disease (>4 stools/day and/or daily presence of blood and/or pus) with minimal systemic symptoms; and (4) severely active disease (>6 bloody stools/day, and evidence of toxicity, as demonstrated by fever, tachycardia, anemia, or an ESR) (note that the stool frequency for remission and mild disease may overlap the upper limit of normal stool frequency) (Table 1).[4,84,85]Toxic (fulminant) colitis occurs when there is extension of mucosal inflammation through all layers of the colonic wall to the serosa and presents clinically as abdominal tenderness to deep palpation. Megacolon is defined as dilatation of the colon ≥7 cm demonstrated by x-ray and presents clinically as abdominal distension, decreased or absent bowel sounds, distended small bowel loops, and in some cases decreased stool frequency.[86]

When identifying patient subpopulations for inclusion in clinical trials, clinical and endoscopic disease activity instruments must be selected and entry criteria developed for each instrument that allow for stratification of patients with clinical remission, mildly active disease, moderately active disease, or severely active disease. In most instances, hospitalized patients with fulminant colitis and/or megacolon are excluded from clinical trials (see Tables 1–6). Frequently, clinical trials of outpatients with active UC evaluate mildly and moderately active UC in the same trial.

Patients with clinical (symptomatic) remission must have endoscopic confirmation of remission; conversely, patients with mildly, moderately, or severely active disease must have endoscopic confirmation of disease activity. Patients treated with topical preparations for left-sided or distal disease should also have confirmation of the disease extent prior to enrollment. Previous studies have evaluated the following treatment indications for patients with UC: treatment of signs and symptoms or induction of remission for mildly to moderately active UC, treatment of signs and symptoms or induction of remission for severely active UC, and maintenance of remission. The Food and Drug Administration (FDA) draft guidelines for the clinical evaluation of drugs for UC indicate that potential indications are as follows: treatment of acute disease, induction of remission (includes a requirement for endoscopic healing), and maintenance of remission.[87]

Classification and Treatment Indications According to Concomitant Therapy

Steroid-dependent UC. Patients who are unable to discontinue corticosteroids without experiencing a symptomatic relapse are considered to be steroid dependent, one form of chronically active UC. The term "steroid-dependency" applies to individuals whose disease flares below a particular dose of steroids and remains asymptomatic only if they continue this medication. Steroid dependency must be distinguished from "maintenance therapy" with a steroid, which applies to treatment with a fixed dose of a steroid for a fixed period of time (6–12 months) to maintain remission. Faubion et al described the clinical course in a population-based cohort of patients with UC from Olmsted County, Minnesota, who received an initial course of corticosteroid therapy.[88] A steroid responsive state was defined as complete or partial clinical response to 40–60 mg/day of prednisone and no worsening of clinical symptoms 30 days after prednisone treatment was completed. A steroid-dependent state was defined as partial or complete clinical response to treatment with prednisone 40–60 mg/day and relapse within 30 days after prednisone treatment was completed or relapse with attempted dose reduction of prednisone resulting in the use of prednisone at doses of ≤15–25 mg/day for at least 6 months. A steroid refractory state was defined as no response to prednisone at doses of 40–60 mg/day within 30 days. It should be recognized that steroid responsiveness requires (1) an adequate daily dose of steroids (defined as 40 mg prednisone in North America or even higher doses in other countries) and (2) an adequate duration of treatment (eg, 4–8 weeks).

Refractory UC. In patients with Crohn's disease, the European Agency for the Evaluation of Medicinal Products defines refractory Crohn's disease as "patients who are uncontrolled on 1 mg/kg prednisolone daily and who require additional immunosuppressive agents to control adequately the activity of the disease" or "patients who have not responded to immunosuppressive drugs."[89] It seems reasonable to define refractory UC similarly, although the steroid dose of 1 mg/kg can clearly be questioned. As stated below, trials in "refractory UC patients" should state the list of drugs and doses to which the patient must have been refractory.

End Points Based on Treatment Indications

Response to Treatment and Induction of Clinical Remission for Mildly to Moderately Active UC

The clinical and composite end points based on the clinical instruments and the composite clinical and endoscopic end points discussed above that have been used for clinical trials in patients with mildly to moderately active UC (and outpatients with moderately to severely active UC) are summarized in Table 1. Clinical trials with topical agents for left-sided and distal colitis generally used the same scores to assess disease activity/treatment success as trials for more extensive colitis. Thus, there is no reason to use different end points based on disease extent.

Initial trials had minimal or no disease activity-based eligibility criteria. This omission led to inclusion of patients with minimal disease activity in whom it is difficult to identify a benefit of treatment. More recent trials have typically restricted entry criteria to select patients with mild to moderate, moderate, or moderate to severe UC. In the 1980s and 1990s, the primary end point for induction trials was often clinical response or improvement. A wide variety of nonvalidated instruments to assess disease activity were used, and the definitions of response or improvement included relative modest changes in disease activity. An undesirable consequence was a high rate of response to placebo. Over the past several years, there has been an evolution to a composite end point of complete symptom resolution and endoscopic (mucosal) healing as the primary end point. Several composite end points have been used to achieve this goal including the definitions of remission used by Rutgeerts et al,[29] Lichtenstein et al,[41] Kamm et al,[42] and Feagan et al.[25] The end points of response corroborated by remission as defined by Rutgeerts et al[29] and Sandborn et al[40] led to regulatory approval by the FDA and were shown to be clinically relevant by demonstrating correlation with IBDQ and SF-36 quality of life scores.

A slight majority of the authors (and the IOIBD members) recommended that the primary end point for therapeutic trials in patients with mildly to moderately active UC (and outpatients with moderately to severely active UC) should be induction of remission, defined as complete symptom resolution and endoscopic (mucosal) healing. Whether clinical symptoms and endoscopic appearance should be incorporated in a single composite score remains a matter of debate. A slight minority of the authors (and IOIBD members) recommended that "response to treatment" of active disease (ie, a reduction in signs and symptoms) be used as the primary end point. Studies evaluating induction of remission (or response) should in general be 4 to 8 weeks in duration, being short enough on one hand to be clinically relevant in patients with active symptoms and long enough on the other hand to allow sufficient time for mucosal healing to occur. For very rapidly acting agents, trials that are shorter in duration may be possible. Slowly acting agents that require more than 8 weeks to demonstrate an effect should in general be considered as maintenance agents rather than induction agents. Reporting the mean or median increase in disease activity scores in a population of patients is not acceptable as a primary end point but may be done as a secondary end point. Studies in patients

with left-sided disease only can use the same end points as the ones developed for more extensive disease.

Response to Treatment and Induction of Clinical Remission for Severely Active UC

The clinical end points based on clinical instruments that have been used for clinical trials in hospitalized patients with severely active UC are summarized in Table 2. Most trials have entered patients with severely active UC as defined by the Truelove and Witts criteria[4] or a Lichtiger score >10 points.[18] Several attempts have been made to add other components to improve selection of patients requiring intensive treatment. Hypoalbuminemia and elevated serum concentrations of C-reactive protein (CRP) have been recognized as biologic markers of disease severity, and several prognostic scores that include these components have been developed.[12,90–93] Travis et al showed that, after 3 days of intensive treatment, 85% of patients with >8 stools/day or CRP >45 mg/L will require colectomy during the same admission.[92] These results were reproduced by another group in Sweden who proposed the Fulminant Colitis Index,[93] calculated according to the following formula: number of bowel movements/day + 0.14 × (CRP >8 mg/L). In this series, 72% of patients with a score >8 went to colectomy. This index was also used to select moderate to severe patients for inclusion in a recent controlled trial of infliximab in UC. Hospitalized patients with a Fulminant Colitis Index >8 on day 3 of intravenous corticosteroid treatment or a Seo activity index >150 on days 5, 6, or 7 met inclusion criteria for the trial and were randomized to infliximab or placebo.[15] Sixty-nine percent of the patient subgroup with a Fulminant Colitis Index value >8 on day 3, and 62% of patients with a Seo index >150 on days 5, 6, or 7, who were treated with placebo had an operation. These data reinforce the predictive value of the Fulminant Colitis Index for early (day 3) selection of patients at high risk of colectomy. These data also underscore that persistence of moderate to severe disease activity despite intravenous steroid therapy for 5 days or more is associated with a high risk of colectomy.

Study designs for severe colitis have evaluated the following: the comparative efficacy of initial therapy with intravenous corticosteroids vs adrenocorticotropic hormone (ACTH), cyclosporine, or infliximab; the adjunctive efficacy of antibiotics or bowel rest with total parenteral nutrition in patients receiving initial therapy with intravenous corticosteroids; and the adjunctive efficacy of cyclosporine, infliximab, or visilizumab in patients failing intravenous corticosteroids. In the 1960s, 1970s, and 1980s, the primary end point for induction trials in patients with severely active UC was typically a composite end point of clinical remission and the ability to be discharged from the hospital. In the 1990s, a less stringent end point, clinical response, defined as a decrease in the Lichtiger Index score to a value of ≤10 points came into use.[18] Recent regulatory discussions with the FDA suggest an evolution back to a more stringent composite end point as defined by (1) decrease from baseline in the total Mayo Score ≥3 points and ≥30% and decrease in the rectal bleeding subscore ≥1 point or an absolute rectal bleeding subscore of 0 or 1 at day 45; (2) mandatory corticosteroid taper (patients who relapse during steroid taper can increase the steroid dose once and then resume tapering) with steroid discontinuation by day 90; (3) maintenance therapy with mesalamine is permitted; and (4) maintenance therapy with azathioprine or 6-mercaptopurine is not permitted before day 45 (to avoid confounding of the assessment of the primary end point).

The authors recommend that the primary end point for therapeutic trials in patients with severely active UC be treatment success based on a composite definition to include both induction of clinical response by day 14 AND induction of clinical remission and endoscopic remission (mucosal healing) at day 90. Patients who are receiving corticosteroids (either as a monotherapy compared with a novel agent or in combination with a novel agent) must undergo a mandatory steroid taper with steroid discontinuation by day 90. The recommendation for clinical and endoscopic remission at day 90 was favored by a slight majority of the authors (and IOIBD members), with the others favoring a recommendation that would permit clinical and endoscopic response (rather than remission) at day 90 as part of the composite primary definition of the primary end point. Patients who require rescue therapy with an increased dose of corticosteroids or other rescue medications for UC prior to day 90 are considered treatment failures. If an additional medication is introduced as a maintenance agent (for instance a slow-acting immunosuppressive agent such as azathioprine), it must be done at a standardized time (ie, at day 0 in all patients, at day 14 in responding patients, and others). Clinical response at day 14 is defined as a decrease in the Lichtiger Index to ≤10 or a decrease from baseline in the total Mayo Score ≥3 points and ≥30% and a decrease in the rectal bleeding subscore ≥1 point or an absolute rectal bleeding subscore of 0 or 1. Clinical remission at day 90 is defined as a decrease in the Lichtiger Index to ≤3 or a total Mayo Score of ≤2 points with no individual subscore >1 point and the mandatory steroid taper with steroid discontinuation. Endoscopic remission (mucosal healing) is defined as absence of friability, blood, erosions, and ulcers in all visualized segments (see below). Reporting the mean or median increase in disease activity scores in a population of patients is not acceptable as a primary end point but may be done as a secondary end point.

Maintenance of Remission

The end points that have been used for assessing maintenance of remission in patients with UC are

Table 1. End Points for Response to Treatment and Induction of Remission for Mildly to Moderately Active Ulcerative Colitis

Author (reference)	Drug	Disease activity	Entry criteria	Instrument and end point	Placebo rate
Truelove[4]	Cortisone (oral)	Mild to severe ulcerative colitis	More than very mild symptoms	Truelove and Witts Severity Index	
				Clinical remission[a]	16%
				Clinical response[b] at 6 weeks	41%
Truelove[108]	Hydrocortisone (enema)	Mild to moderate distal colitis	Active symptoms confirmed by endoscopy	Clinical remission (symptom free) at 1 week	5%
Hanauer[21]	Budesonide (enema)-Entocort Enema	Mild to moderate distal colitis	At least one of frequency and urgency of stools, diarrhea, or grossly visible blood, confirmed by sigmoidoscopic inflammation grade score ≥2	Physicians Global Evaluation	
				Remission[c] at 6 weeks	4%
Baron[109]	Sulfasalazine	Mild to moderate ulcerative colitis	Typical symptoms, confirmed by endoscopy	Clinical remission[d]	5%
				Clinical response[e] at 3 weeks	35%
Sutherland[30]	Mesalamine (enema)-Rowasa Enema[hh]	Mild to moderate distal colitis	Sutherland Index score ≥3, confirmed by endoscopy	Sutherland Index	
				Decrease in Sutherland Index score[f]	−22%
				Clinical improvement[g] at 6 weeks	22%
Williams[110]	Mesalamine (suppository)-Rowasa Suppository-Trial 1	Mild to moderate ulcerative proctitis	Sutherland Index score ≥3, confirmed by endoscopy	Sutherland Index	
				Decrease in Sutherland Index score[f]	−37%
				Clinical improvement[g] at 6 weeks	41%
Williams[110]	Mesalamine (suppository)-Rowasa Suppository-Trial 2	Mild to moderate ulcerative proctitis	Sutherland Index score ≥ 3, confirmed by endoscopy	Sutherland Index	
				Decrease in Sutherland Index score[f]	−34%
				Clinical improvement[g] at 6 weeks	26%
Schroeder[26]	Mesalamine (oral)-Asacol[ii]	Mild to moderate ulcerative colitis	Not stated	Mayo Score	
				Complete response[h]	5%
				Partial + complete response[ii] at 6 weeks	18%
Sninsky[31]	Mesalamine (oral)-Asacol[ii]	Mild to moderate ulcerative colitis	Active signs and symptoms	Mayo Score	
				Remission[h]	5%
				Improvement + remission[j] at 6 weeks	23%
Rachmilewitz[10]	Mesalamine (oral)-Claversal[jj] Sulfasalazine	Mild to moderate ulcerative colitis	Clinical Activity Index Score ≥6, Endoscopic Index Score ≥4	Clinical Activity Index	No placebo group
				Remission[j] at 8 weeks	
Hanauer[17]	Mesalamine (oral)-Pentasa	Mild to moderate ulcerative colitis	Clinical symptoms, Sigmoidoscopic Index Score ≥5	Physicians Global Assessment	
				Treatment success[k]	54%
				Treatment benefit[l]	36%
				Remission[m] at 8 weeks	12%
Anonymous[111]	Mesalamine (oral)-Pentasa[kk]	Mild to moderate ulcerative colitis	Not stated	Physicians Global Assessment	
				Remission[n] at 8 weeks	12%
Lichtenstein[41]	Mesalamine (oral)-SDP476[ll]	Mild to moderate ulcerative colitis	Sutherland Index score 4−10	Sutherland Index	
				Remission[o] at 8 weeks	13%
Kamm[42]	Mesalamine (oral)-SDP476[ll]	Mild to moderate ulcerative colitis	Sutherland Index score 4−10	Sutherland Index	
				Remission[o]	22%
				Clinical remission[p]	22%
				Clinical improvement[q] at 8 weeks	40%
Kruis[71]	Mesalamine (oral)-Salofalk Pellets[mm]	Mild to moderate ulcerative colitis	Clinical Activity Index Score 6−12, Endoscopic Index Score ≥4	Clinical Activity Index	No placebo group
				Clinical remission[j]	
				Clinical improvement[r] at 8 weeks	
Marteau[112]	Mesalamine (oral + rectal)	Mild to moderate ulcerative colitis	Sutherland Index score 3−8	Remission[s]	No placebo group
	Mesalamine (oral>			Improvement[t] at 8 weeks	
Levine[24]	Balsalazide-Colazal	Mild to moderate ulcerative colitis	Active ulcerative colitis confirmed by endoscopy	Improvement based on individual symptom scores[u] at 8 weeks	No placebo group
Sandborn[113]	Nicotine (transdermal)	Mild to moderate ulcerative colitis	Active ulcerative colitis	Mayo Score	
				Clinical remission[v]	0%
				Clinical improvement[w] at 4 weeks	9%
Sandborn[33]	Cyclosporine (enema)	Mild to moderate ulcerative colitis	Active ulcerative colitis	Mayo Score	
				Clinical remission[v]	5%
				Clinical improvement[w] at 4 weeks	45%
Sinha[114]	Epidermal growth factor (enema)	Mild to moderate ulcerative colitis	Powell-Tuck Index score ≥5	Powell-Tuck Index	
				Remission[x]	25%
				Sutherland Index	8%
				Remission[y] at 2 weeks	
Van Deventer[115]	Alicaforsen (enema)[nn]	Mild to moderate distal colitis	Mayo Score 3−10	Mayo Score	
				Decrease in Mayo Score at 4 weeks	−28%
Sandborn[35]	Repifermin[oo]	Mild to moderate ulcerative colitis	Mayo Score 3−10	Mayo Score	
				Remission[z]	11%
				Response[w]	36%
				Clinical response[aa] at 4 weeks	39%

Table 1. (Cont'd)

Author (reference)	Drug	Disease activity	Entry criteria	Instrument and end point	Placebo rate
Van Assche[36]	Daclizumab-Zenepax[pp]	Moderate ulcerative colitis	Mayo Score 5−10	Mayo Score	
				Remission[z]	10%
				Response[w]	44%
				Clinical response[aa] at 8 weeks	49%
Feagan[25]	Anti-α4β7 integrin antibody-MLN-02[qq]	Moderate ulcerative colitis	Ulcerative colitis clinical score 5−9, stool frequency or rectal bleeding subscore ≥1, modified Baron sigmoidoscopy score ≥2	Ulcerative Colitis Clinical Score	
				Clinical remission[bb]	14%
				Clinical response[cc] at 6 weeks	33%
Rutgeerts and Sandborn ACT 1[29]	Infliximab-Remicade[rr]	Moderate to severe ulcerative colitis	Mayo Score 6−12, endoscopy subscore ≥2	Mayo Score	
				Clinical response[dd]	37%
				Clinical remission[ee] at 8 weeks	15%
Rutgeerts and Sandborn ACT 2[29]	Infliximab-Remicade[rr]	Moderate to severe ulcerative colitis	Mayo Score 6−12, endoscopy subscore ≥2	Mayo Score	
				Clinical response[dd]	29%
				Clinical remission[ee] at 8 weeks	6%
Tilg[116]	Pegylated interferon α[ss]	Mild to moderate ulcerative colitis	Clinical Activity Index Score >6 despite prednisone 10−40 mg daily	Clinical Activity Index	
				Remission[ff] at 12 weeks	35%
Musch[117]	Interferon-β-1a	Moderate ulcerative colitis	Clinical Activity Index Score ≥8, acute lesions at endoscopy	Clinical Activity Index	
				Response[gg]	34%
				Complete response[ff] at 8 weeks	38%

[a]Clinical remission was defined as 1 or 2 stools per day without blood, no fever, no tachycardia, hemoglobin normal or returning towards normal, sedimentation rate normal or returning towards normal, and gaining weight. To be included in this category, the patient was expected to show all of the above features. No change or worse was described as "self-explanatory." All intermediate cases were defined as improved.
[b]Clinical response defined as improved or clinical remission.
[c]Remission defined as ≤3 bowel movements per day; no blood in stools; no symptoms of urgency, abdominal pain, or painful evacuations; and a sigmoidoscopic inflammation grade score of 0.
[d]Clinical remission was defined as no symptoms.
[e]Clinical response defined as improved or clinical remission. All other patients classified as no change or worse.
[f]Percentage change from baseline calculated by taking the average of the percentage change from baseline for each individual patient.
[g]Clinical improvement defined as "much improved."
[h]Complete response (remission) defined as complete resolution of: (1) stool frequency (normal stool frequency); (2) rectal bleeding (no rectal bleeding); (3) patients functional assessment score (generally well); (4) endoscopy findings (normal); AND a Physicians Global Assessment score of 0.
[i]Treatment success is defined as either a complete response (remission)[h] or a partial response (improvement) to therapy. A partial response (improvement) to therapy is defined as the following: improvement in the baseline Physicians Global Assessment score AND improvement in at least one other clinical assessment (stool frequency, rectal bleeding, patients functional assessment, endoscopy findings) AND no worsening in any other clinical assessment.
[j]Remission defined as a Clinical Activity Index score ≤4.
[k]Treatment success defined as a Physician's Global Assessment score of 1 or 2.
[l]Treatment benefit defined as any improvement of Physician's Global Assessment score over baseline.
[m]Remission defined as a Physician's Global Assessment score of 1.
[n]Remission defined as resolution of symptoms plus score of "1" on one of endoscopic components (mucosal vascular pattern, erythema, granularity, or friability) and "0" for others.
[o]Remission defined as a Sutherland Index score ≤1 with a score of 0 for rectal bleeding and stool frequency and at least a 1-point reduction in baseline sigmoidoscopy score.
[p]Clinical remission defined as a complete resolution of symptoms.
[q]Clinical improvement defined as a drop in the Sutherland Index Score ≥3 points.
[r]Clinical improvement defined as a decrease in the Clinical Activity Index score ≥3.
[s]Remission defined as a Sutherland Index Score <2.
[t]Improvement defined as a decrease in the Sutherland Index ≥2 points.
[u]Improvement defined as a reduction from baseline of ≥1 grade in rectal bleeding and at least one of the other assessed symptoms.
[v]Clinical remission defined as a Mayo Score of 0.
[w]Clinical improvement (response) defined as a decrease in the Mayo Score ≥3 points.
[x]Remission defined as a Powell-Tuck Index score ≤4 and no inflammation on sigmoidoscopy.
[y]Remission defined as a Mayo Score of 0 or 1 and no blood in the stool.
[z]Remission defined as a Mayo Score of 0 on the sigmoidoscopy and bleeding components and a score of 0 or 1 on the stool frequency and Physician's Global Assessment components.
[aa]Clinical response defined as a decrease in the Mayo Score ≥2 points without the endoscopy component.
[bb]Clinical remission defined as an ulcerative colitis clinical score of 0 or 1 and a modified Baron Score of 0 or 1 and no rectal bleeding.
[cc]Clinical response defined as an improvement of 3 points or more on the ulcerative colitis clinical score.
[dd]Clinical response defined as a decrease in the Mayo Score of at least 30% and 3 points or more, plus a decrease in the rectal bleeding subscore of at least 1 or a rectal bleeding subscore of 0 or 1.
[ee]Clinical remission defined as a Mayo Score of 2 or less with no individual subscore greater than 1.
[ff]Remission (complete response) defined as a Clinical Activity Index score of 4 points or less.
[gg]Response defined as a decrease in the Clinical Activity Index score of 6 points or more.
[hh]Rowasa, Solvay, Brussels, Belgium.
[ii]Asacol, Procter and Gamble, Cincinnati, OH.
[jj]Claversal, Smith Kline Beecham, Bentford, UK.
[kk]Pentasa, Ferring, Copenhagen, Denmark.
[ll]SPD476, SHIRE, Basingstoke, UK.
[mm]Salofalk, DrFalk Pharma, Freiburg, Germany.
[nn]Alicaforsen, ISIS Pharmaceuticals, Seattle, WA.
[oo]Repifermin, HumanGenome Sciences, Rockville, MD.
[pp]Daclizumab-Zenepax, PDL Biopharma, Fremont, CA.
[qq]MLN-02, Millenium, Cambridge, MA.
[rr]Infliximab-Remicade, Centocor, Malvern, PA.
[ss]Pegylated interferon, Schering-Plough, Kennilworth, NJ.

Table 2. End Points for Response to Treatment and Induction of Remission in Hospitalized Patients With Severely Active Ulcerative Colitis

Author (reference)	Drug	Disease activity	Entry criteria	Instrument and end point	Placebo rate
Truelove[118]	Prednisolone (intravenous)	Severe ulcerative colitis	Severe ulcerative colitis using the Truelove and Witts Severity Index definition[a]	Truelove and Witts Severity Index Clinical remission[b] Clinical response[c] at 5 days	No placebo group
Jarnerot[119]	Betamethasone (intravenous)	Severe ulcerative colitis	Severe ulcerative colitis using the Truelove and Witts Severity Index definition[a]	Remission[d] at 5 days	No placebo group
Kaplan[120]	Hydrocortisone (intravenous) or ACTH (intravenous)	Severe ulcerative colitis	Admission to the hospital for acute ulcerative colitis and requirement for intravenous corticosteroids	Therapeutic success (clinical remission)[e] at 5-10 days	No placebo group
Powell-Tuck[121]	Hydrocortisone (intravenous) or ACTH (intramuscular)	Severe ulcerative colitis	Admission to the hospital for severe ulcerative colitis	Discharge from the hospital without colectomy at this admission	No placebo group
Meyers[122]	Hydrocortisone (intravenous) or ACTH (intravenous)	Severe ulcerative colitis	Severe or fulminant ulcerative colitis[f]	Therapeutic success[g] at 10 days	No placebo group
Dickinson[123]	Vancomycin (oral) as an adjunct to intravenous prednisolone	Moderate or severe ulcerative colitis	Admission to the hospital for moderate to severe ulcerative colitis using the Truelove and Witts Severity Index definition[a]	Discharge from the hospital without colectomy at this admission	61%
Chapman[91]	Metronidazole (intravenous) as an adjunct to intravenous prednisolone	Severe ulcerative colitis	Severe ulcerative colitis using the Truelove and Witts Severity Index definition[a]	Decisive improvement (remission)[h] at 5 days	70%
Mantzaris[124]	Tobramycin + metronidazole (intravenous) as an adjunct to intravenous hydrocortisone	Severe ulcerative colitis	Severe ulcerative colitis using a modified Truelove and Witts Severity Index definition[9]	Decisive improvement (remission)[h] after 10 days	65%
Mantzaris[125]	Ciprofloxacin (intravenous) as an adjunct to intravenous hydrocortisone	Severe ulcerative colitis	Severe ulcerative colitis using a modified Truelove and Witts Severity Index definition[i]	Decisive improvement (remission)[8] after 10 days	77%
Dickinson[126]	Total parenteral nutrition and bowel rest as an adjunct to intravenous prednisone	Moderate or severe ulcerative colitis	Admission to the hospital for moderate to severe ulcerative colitis using the Truelove and Witts Severity Index definition[a]	Reduction in prednionse from 40 mg/day to 10 mg/day and discharge from the hospital without colectomy at this admission	50%
McIntyre[127]	Total parenteral nutrition and bowel rest as an adjunct to intravenous prednisolone	Severe ulcerative colitis	Admission to the hospital for severe ulcerative colitis	Discharge from the hospital without colectomy at this admission	40%
Lichtiger[18]	Cyclosporine (intravenous) as an adjunct to intravenous corticosteroids	Severe ulcerative colitis	Lichtiger Index score ≥12 points after ≥10 days of intravenous hydrocortisone	Lichtiger Index Clinical improvement[j] Treatment success[k] after treatment for ≥ 10 days and discharge from the hospital without colectomy at this admission	No placebo group
Lichtiger[19]	Cyclosporine (intravenous) as an adjunct to intravenous corticosteroids	Severe ulcerative colitis	Lichtiger Index score ≥10 points after ≥7 days of intravenous corticosteroids	Lichtiger Index Response[l] After treatment for ≤14 days and discharge from the hospital without colectomy at this admission	0%
D'Haens[128]	Cyclosporine (intravenous) or methyl-prednisolone (intravenous)	Severe ulcerative colitis	Admission to the hospital for severe ulcerative colitis and Lichtiger Index score ≥10 points	Lichtiger Index Response[m] at day 8	No placebo group
Van Assche[129]	Cyclosporine (intravenous) 2 mg/kg or 4 mg/kg	Severe ulcerative colitis	Admission to the hospital for severe ulcerative colitis and Lichtiger Index score ≥10 points	Lichtiger Index Response[m] at day 8	No placebo group
Sands[130]	Infliximab (intravenous) as an adjunct to intravenous corticosteroids	Severe ulcerative colitis	Lichtiger Index score ≥10 points and moderate to severe endoscopic changes after ≥5 days of intravenous corticosteroids	Lichtiger Index Treatment success[n] at 2 weeks	0%
Ochsenkuhn[131]	Prednisolone (intravenous) or infliximab (intravenous)	Severe ulcerative colitis	Lichtiger Index score ≥10 points	Lichtiger Index Treatment success[o] at 3 and 13 weeks Remission[p] at 3 and 13 weeks	No placebo group

Table 2. (Cont'd)

Author (reference)	Drug	Disease activity	Entry criteria	Instrument and end point	Placebo rate
Jarnerot[15]	Infliximab (intravenous) as an adjunct to intravenous corticosteroids	Moderate to severe ulcerative colitis	Severe disease at day 3 or moderate disease at day 5, 6, or 7 after starting intravenous corticosteroids[q]	Death or colectomy within 90 days	33%
Targan[20]	Visilizumab (intravenous) as an adjunct to intravenous corticosteroids	Severe ulcerative colitis	Lichtiger Index score ≥10 points after ≥5 days of intravenous corticosteroids	Lichtiger Index Response[l] Remission[r] Specific time not specified	No placebo group

ACTH, adrenocorticotropic hormone.
[a]Severe ulcerative colitis defined as severe diarrhea (6 or more movements a day) with macroscopic blood in stools. Fever (mean evening temperature more that 99.5°F [37.5°C] or a temperature of 100°F [37.8°C] or more on at least 2 days out of 4). Tachycardia (mean pulse rate more than 90 per minute). Anemia (hemoglobin 75% or less, allowance made for recent transfusion). ESR significantly raised (more than 30 mm in 1 hour).
[b]Clinical remission was defined as 1 or 2 stools per day without blood, no fever, no tachycardia, hemoglobin normal or returning towards normal, sedimentation rate normal or returning towards normal, and gaining weight. To be included in this category, the patient was expected to show all of the above features. No change or worse was described as "self-explanatory." All intermediate cases were defined as improved.
[c]Clinical response defined as improved or clinical remission.
[d]Remission was defined as absence of bowel symptoms and sigmoidoscopy without any signs of active disease such as edema, ulceration, contact or spontaneous bleeding with visible vascular pattern.
[e]Therapeutic success (clinical remission) was defined as 1 or 2 bowel movements per day without blood, no fever or tachycardia, hemoglobin normal or returning to normal, and weight gain.
[f]Severe ulcerative colitis was defined as one or more episodes of abdominal tenderness, 9 or more bowel movements per day, pulse rate of 100 or more, or body temperature ≥37.5°C after 24 hours of in patient observation while maintaining the prior ambulatory program of medical therapy. Fulminant ulcerative colitis was defined as more than 9 bowel movements per day, as well as a temperature >38°C or colonic dilation (diameter ≥6.0 cm) on plain abdominal x-ray or both.
[g]Therapeutic success was defined as absence of all symptoms and the reduction of the frequency of bowel movements to 2 or less per day.
[h]Decisive improvement (remission) defined as 3 or less formed or forming stools daily, absence of rectal bleeding, and absence of clinical signs of severity such as pyrexia and/or tachycardia.
[i]Severe ulcerative colitis defined as more than 8 bowel movements daily and presentation with fever (>37.5°C), tachycardia (pulse >100), raised ESR (>30 mm/hour), and either low serum albumin (<3.5 g/L) or anemia (hemoglobin <10 g/dL) or both.
[j]Clinical improvement defined as a decrease from baseline in the Lichtiger Index score ≥50%.
[k]Treatment success defined as maintenance of clinical improvement after conversion from intravenous hydrocortisone and cyclosporine to oral forms and discharge from the hospital without colectomy.
[l]Response defined as a Lichtiger Index score <10 points for 2 consecutive days.
[m]Response defined as a Lichtiger Index score <10 points on days 7 and 8 with a drop in the score from baseline of at least 3 points and discharge of the patient from the hospital.
[n]Treatment success defined as absence of all of the following 4 criteria: (1) failure to achieve a clinical response as defined by a Lichtiger Index score <10 and a 5-point reduction compared with baseline; (2) treatment with corticosteroids >60 mg/day or cyclosporine or other immunomodulators because of no improvement or worsening clinical condition; (3) if the patient underwent a nonelective colectomy; or (4) if the patient died as a result of chronic ulcerative colitis.
[o]Treatment success defined as clinical response (decrease in Lichtiger Index score >5 points from baseline score and to a score <10 points) after 3 weeks as well as after 13 weeks and no need to start or increase high-dose prednisolone or to perform colectomy.
[p]Remission defined as the absence of inflammatory symptoms (rectal bleeding or diarrhea) in conjunction with mucosal healing (absence of ulceration, significant granularity, or friability).
[q]Patients requiring hospitalization for moderate to severe disease defined as an Activity Index (Seo Index) score ≥150 points and treatment with intravenous corticosteroids. In addition, patients were required to have severe disease as defined by Fulminant Colitis Index score[92] ≥8 points at day 3 or moderate disease at days 5, 6, or 7 as defined by an Activity Index score ≥150 points at day 5, 6, or 7 after starting intravenous corticosteroids.
[r]Remission defined as a Lichtiger Index score ≤3 points for 2 consecutive days.

summarized in Table 3. Most trials have enrolled patients with clinical remission ± endoscopic remission. The duration of such trials has typically been 6 or 12 months. More recently, 2 studies enrolled patients with active UC and included both an early induction of response and remission end point at 8 weeks and late maintenance of response and remission at 6 and 12 months.[29] In other disease settings, the time to relapse (survival analysis) has been used to measure maintenance of remission. Such an approach may be reasonable in patients with UC, but the absolute increase in the time to relapse that would be clinically significant has not been determined.

The authors recommend that patients with UC enrolled in maintenance trials be both in clinical remission (no clinical symptoms) and endoscopic remission (mucosal healing) and that the primary end point for maintenance trials should be (absence of) clinical relapse (increase in stool frequency ≥1 or 2 stools above normal for the patient and recurrence of rectal bleeding) confirmed by endoscopy. The criteria for "relapse" should be predefined with the score to be used in an individual study. An acceptable alternative study design is to enroll patients with active UC and have both an early induction of response and remission end point at 4–8 weeks and a late maintenance of response and remission at 6 months or later. Studies evaluating maintenance of remission should be at least 6 months in duration. To limit the sample size of these trials, recruitment of patients could be restricted to those with a certain "tendency to relapse," eg, with at least 1 clinical relapse per year prior to inclusion.

Corticosteroid Sparing

The end point of corticosteroid sparing is difficult to define. Studies that have enrolled patients with corticosteroid-induced remission, corticosteroid-dependent disease, and corticosteroid refractory disease are summarized in Table 4. Distinguishing between corticosteroid dependence and symptoms of adrenal insufficiency may be difficult in some patients who have received prolonged corticosteroid treatment. For patients with corticoste-

Table 3. End Points for Maintenance Remission for Ulcerative Colitis

Author (reference)	Drug	Disease activity	Entry criteria	End point	Placebo relapse rate
Misiewicz[132]	Sulfasalazine	Remission	Clinical and sigmoidoscopy remission	Clinical relapse[a] Sigmoidoscopy relapse[b] at 1 year	76% 92%
Riis[133]	Sulfasalazine	Remission	Clinical remission	Clinical relapse[c] 6 months	29%
Dissanayake[134]	Sulfasalazine	Remission	Clinical, sigmoidoscopy, and histology remission	Clinical relapse confirmed by sigmoidoscopy at 6 months	55%
Riley[135]	Sulfasalazine vs mesalamine	Remission	Remission[d]	Clinical relapse confirmed by sigmoidoscopy[e] at 1 year	No placebo group
Mulder[136]	Sulfasalazine vs mesalamine	Remission	Clinical, sigmoidoscopy, and histology remission	Clinical, sigmoidoscopy or histology relapse at 1 year	No placebo group
Hanauer[137]	Mesalamine	Remission	Clinical and sigmoidoscopy remission[f]	Sigmoidoscopy relapse[g] at 6 months	48%
Miner[138]	Mesalamine	Remission	Clinical and sigmoidoscopy remission[h]	Clinical relapse confirmed by sigmoidoscopy[i] at 1 year	38%
Wright[139]	Olsalazine	Remission	Without symptoms[j]	Clinical relapse[k] at 1 year	60%
Ireland[140]	Olsalazine vs sulfasalazine	Remission	Clinical and sigmoidoscopy remission[l]	Clinical relapse confirmed by sigmoidoscopy[m] at 6 months	No placebo group
Kruis[141]	Balsalazide vs mesalamine	Remission	CAI <6 points and an endoscopic index <4 points	Clinical Activity Index Relapse defined as a CAI ≥6 points and an EI score ≥4 points at 6 months	No placebo group
Marteau[142]	Mesalamine suppositories	Remission	Clinical and sigmoidoscopy remission[n]	Clinical and endoscopy relapse[o] at 1 year	62%
Hanauer[143]	Mesalamine suppositories	Remission	Sutherland Index score = 0	Sutherland Index Relapse[p] at 12 months	86%
Thomas[144]	Transdermal nicotine	Remission	Clinical and sigmoidoscopy remission[q]	Endoscopic relapse[r] at 6 months	43%
Kruis[101]	*Escherichia coli* Nissle 1917 vs mesalamine	Remission	Clinical endoscopy and histology remission[s]	Clinical Activity Index Relapse[t] at 12 months	No placebo group
Hawthorne[145]	Azathioprine	Azathioprine induced remission	No steroids and Baron score of 0 or 1	Relapse[u] at 12 months	59%
Rutgeerts and Sandborn Act 1[29]	Infliximab	Moderate to severe ulcerative colitis	Mayo Score 6–12, endoscopy subscore ≥2 despite steroids or azathioprine	Mayo Score Clinical response[v] and Clinical remission[w] at 12 months	20% 17%
Rutgeerts and Sandborn Act 2[29]	Infliximab	Moderate to severe ulcerative colitis	Mayo Score 6–12, endoscopy subscore ≥2 despite steroids, azathioprine, or mesalamine	Mayo Score Clinical response[v] and Clinical remission[w] at 6 months	26% 11%

[a]Clinical relapse defined as diarrhea or blood or mucus in the stool.
[b]Sigmoidoscopy relapse defined as a Baron Score ≥2 points.
[c]Clinical relapse defined as rectal bleeding for more than 3 successive days or more than 3 defecations daily for more than 5 successive days.
[d]Remission defined as the absence of blood in the stool for at least 1 month prior to the trial and sigmoidoscopic appearance of either normal mucosa or only erythema on sigmoidoscopy (Baron Score 0 or 1 points).
[e]Clinical relapse defined as symptomatic deterioration confirmed by an increased sigmoidoscopy grade as measured by the Baron Score.
[f]Clinical remission and sigmoidoscopy remission defined as the passage of 5 or fewer bloodless stools per day for at least 1 month and a score of 0 on the following proctosigmoidoscopic grading scale. 0 = normal or mild granularity, edema hyperemia, or erythema; mildly diminished vascular markings. 1 = mild granularity, edema, hyperemia, or erythema; mildly diminished vascular markings plus friability. 2 = marked erythema or granularity; no vascular markings; bleeding with minimal trauma; no ulcerations. 3 = spontaneous bleeding; ulcerations.
[g]Sigmoidoscopy relapse defined as a proctosigmoidoscopic grade ≥1 point (using the grading system described above in footnote *f*).
[h]Clinical and sigmoidoscopy remission defined as a Sigmoidoscopic Index (see above)[17] <5 points, a mean of less than 5 bowel movements per day, and the absence of rectal bleeding.
[i]Clinical relapse confirmed by sigmoidoscopy using a 3-part definition. The third definition was used only if patients did not satisfy recurrence definitions 1 or 2: (1) a Sigmoidoscopic Index of ≥5 points and one or more of the following: a mean of ≥5 trips to the toilet for 3 of 7 continuous days or the presence of rectal bleeding for 3 of 7 continuous days; (2) a sigmoidoscopic index of ≥5 points with missing data for trips to the toilet or rectal bleeding, at end of study or final study visit; and (3) missing data for the final Sigmoidoscopic Index and early termination from the trial because of insufficient therapeutic effect.
[j]Without symptoms defined as formed stool with no blood or mucus for not less than 1 week and not more than 1 month.
[k]Clinical relapse defined as a relapse of diarrhea (with or without blood or mucus) thought by the attending physician to warrant introduction of rectal or oral corticosteroids.
[l]Clinical and sigmoidoscopy remission defined as an absence of colitis together with an absence of inflammation on sigmoidoscopy.
[m]Clinical relapse confirmed by sigmoidoscopy defined as increased stool frequency with or without blood or mucus and with evidence of inflammation on sigmoidoscopy.
[n]Clinical and sigmoidoscopy remission defined as no rectal bleeding, no mucus in the stools, no diarrhea, no pain, and no tenesmus and an endoscopy score of 0 or 1. Endoscopic severity scored as follows: 0 = normal mucosa or erythema; 1 = granularity or edema or lack of the normal vascular pattern; 2 = contact bleeding; 3 = spontaneous bleeding; 4 = superficial ulcerations; 5 = deep ulcers.
[o]Clinical and endoscopy relapse defined as the occurrence of clinical symptoms with an increase in the endoscopy score (as defined above in footnote *n*) ≥1 point compared with the endoscopy score at entry or occurrence of rectal bleeding more than twice in one day.
[p]Relapse defined as symptoms of rectal bleeding or increase in stool frequency for ≥1 week and endoscopic evidence of inflammation on the individual Sutherland Index scales.
[q]Clinical and sigmoidoscopy remission defined as no recent symptoms and sigmoidoscopic findings of normal mucosa or edema (grades 0 or 1)[146] and an endoscopy score of 0 or 1.
[r]Endoscopy relapse defined as sigmoidoscopic findings of granular friable mucosa (grade 2) or fulminating disease (grade 4).[146]
[s]Clinical, endoscopy, and histology remission defined as a CAI score ≤4 points, an EI score ≤4 points, and no signs of acute inflammation on histologic examination.
[t]Relapse defined when all 3 of the following criteria were met: (1) a CAI score >6 points or an increase in the CAI ≥3 points with a CAI score = 4 points at the same time; (2) an EI score >4 points; (3) histologic signs of acute inflammation.
[u]Relapse defined as worsening symptoms recognized by the patient as active disease (such as rectal bleeding, loose movements, or bowel frequency) with a sigmoidoscopic appearance of grade 1 or above on the Baron Score, or grade 2 or 3 appearance on the Baron Score regardless of symptoms.
[v]Clinical response defined as a decrease in the Mayo Score of at least 30% and 3 points or more, plus a decrease in the rectal bleeding subscore of at least 1 or a rectal bleeding subscore of 0 or 1.
[w]Clinical remission defined as a Mayo Score of 2 or less with no individual subscore greater than 1.

Table 4. End Points for Steroid Sparing for Ulcerative Colitis

Author (reference)	Drug	Disease activity	Entry criteria	Instrument and end point	Placebo relapse rate
Jewell[147]	Azathioprine as adjunctive therapy to corticosteroids	Steroid treated	Mild to severe ulcerative colitis requiring inpatient or outpatient therapy with corticosteroids	Relapse[a] during or after mandatory steroid taper at 1 year	25%
Rosenberg[148]	Azathioprine	Steroid dependent	Active ulcerative colitis and prednisone ≥10 mg per day for at least 3 months	Discontinuation of prednisone at 6 months	7%
Kirk[149]	Azathioprine	Steroid refractory	Active ulcerative colitis despite steroid therapy	Reduction in baseline prednisolone dose at 6 months	−23%
Mantzaris[150]	Olsalazine as an adjunctive therapy to azathioprine	Steroid dependent	Active steroid-dependent ulcerative colitis that responded (Mayo Score ≤2) to induction therapy with prednisolone, azathioprine, and olsalazine	Sutherland Index Relapse[b] during or after mandatory steroid taper at 2 years	No placebo group
Ardizzone[151]	Azathioprine vs mesalamine	Steroid dependent	Active ulcerative colitis and prednisone ≥10 mg per day for at least 6 months	Powell-Tuck Index and Baron Index Treatment success[c] and discontinuation of prednisolone at 6 months	No placebo group
Rutgeerts and Sandborn ACT 1[29]	Infliximab-Remicade	Moderate to severe ulcerative colitis	Mayo Score 6−12, endoscopy subscore ≥2	Mayo Score Clinical remission[d] and discontinuation of steroids at 30 and 54 weeks	10% 9%
Rutgeerts and Sandborn ACT 2[29]	Infliximab-Remicade	Moderate to severe ulcerative colitis	Mayo Score 6−12, endoscopy subscore ≥2	Mayo Score Clinical remission[d] and discontinuation of steroids at 30 weeks	3%

[a]Relapse defined as occurrence of diarrhea with blood in the bowel movements and with sigmoidoscopic evidence of inflammation.
[b]Relapse defined as new symptoms sufficiently severe to warrant treatment with steroids in view of an abnormal sigmoidoscopy (UCDAI >3 points).
[c]Treatment success defined as a composite of induction of clinical remission according to the Powell-Tuck Index, induction of endoscopic remission according to the Baron Index (score ≤1 point), and discontinuation of prednisolone at the end of the study (6 months).
[d]Clinical remission defined as a Mayo Score of 2 or less with no individual subscore greater than 1.

roid-induced remission or corticosteroid refractory disease, corticosteroid sparing requires clinical remission (complete symptom resolution) after combined steroid/investigational drug induction therapy and then maintenance of clinical remission (no clinical symptoms) with complete corticosteroid withdrawal. For patients with corticosteroid-dependent disease, corticosteroid sparing requires that clinical remission (no clinical symptoms) be maintained in spite of complete corticosteroid withdrawal. The minimal clinically significant corticosteroid-free interval following their withdrawal is unclear. However, in Crohn's disease, the FDA required a minimum of 6 months without the need to reintroduce corticosteroids,[94] whereas the European Agency for the Evaluation of Medicinal Products has suggested a minimum of 3 months.[89] An indication for steroid sparing has been granted by the FDA for a 30-week end point in which patients receiving steroids began tapering the steroid dose after week 8 and tapered over as long as 9 weeks (ie, patients could have been steroid free for as little as 13 weeks).[29]

The authors recommend that a clinically meaningful primary end point for therapeutic trials in patients who have a steroid-induced remission (complete resolution of symptoms) should be complete removal of corticosteroids without developing a clinical relapse (clinical symptoms) for at least 3 months. Reduction in the mean average daily dose of corticosteroids is a relevant secondary end point.

Refractory UC

The end point of refractory disease is difficult to define. To date, only one study has limited enrollment to patients who had no response to or could not tolerate corticosteroids and/or azathioprine or 6-mercaptopurine (the ACT 1 trial with infliximab).[29] Infliximab received regulatory approval in the United States for patients with "an inadequate response to conventional therapy," which was not specifically defined. Thus, the pivotal studies of infliximab included heterogeneous patient populations that did not uniformly meet the definition of refractory UC (see above).

The authors believe that targeting refractory UC is problematic because the definition is susceptible to ongoing change. For example, because infliximab is now proven to be efficacious, does refractory disease require patients to be refractory to infliximab? The authors recommend that, if a refractory population of patients is targeted for study enrollment, then the list of drugs that the study population is refractory to must be specified in the entry criteria. Furthermore, entry criteria must require that patients have taken a dose of the drug proven to be effective and for an interval exceeding the time to onset of action. Finally, all patients enrolled in the study must be refractory to the specified drug. An alternative approach is to stratify patients according to whether or not they are refractory to a given drug or group of drugs.

Endoscopic Remission

The end points for endoscopic response and remission that have been used in clinical trials of patients with active UC are summarized in Table 5 and for remission maintenance in Table 3. An endoscopic end point, be it included in a composite score or assessed in a separate score, is recommended in types of clinical trials and both should be incorporated into the primary end point. In one study, patients who entered with a Mayo endoscopy subscore of 2 or 3 and achieved an endoscopy subscore of 0 or 1 (mucosal healing) at week 8 predicted clinical remission at week 8 and a lower risk of relapse at week 30 than patients with an endoscopy subscore of 2 or 3 at week 8.[95] Patients with endoscopic remission should not have any mucosal friability (this definition requires modification of the Mayo Score, the Sutherland Index, and the Baron Score as discussed above). Reporting the mean or median decrease in endoscopy activity scores in a population of patients is not acceptable as the sole measure of endoscopic response but may be done as a secondary end point in conjunction with the determination of endoscopic response and remission.

The authors recommend that endoscopic findings be incorporated into the primary end point and that endoscopic response and remission be determined as secondary end points. Absence of friability, blood, erosions, and ulcers in all visualized segments are the required components of genuine endoscopic healing. An abnormal vascular pattern in the absence of these other features is still compatible with endoscopic healing If photographic documentation is used, pictures must be taken at the same distance above the anal margin on every occasion but also in the most severely affected segment (if these 2 do not coincide). In studies evaluating the topical treatments for distal UC with suppositories, foams, or enemas, examination of colonic mucosa above the endoscopic proximal limit of disease should be performed. The use of a set of "endoscopic examples pictures" to help the endoscopist in grading the severity of lesions can be extremely helpful and should be encouraged (and this approach should be formally validated).

Histologic Remission

Histologic changes usually lag behind clinical and endoscopic improvement and, therefore, are not generally used for clinical decision making. However, the information provided by microscopic analysis of colonic mucosal biopsy specimens should be used as supportive data. The end points for histologic remission that have been used in clinical trials of patients with active UC are summarized in Table 6. The end points for histologic remission have not been well-defined in most studies. Instead, studies have reported the mean or median decrease in a population of patients. This is not optimal, and, ultimately, studies seeking to demonstrate histologic remission will need to define a cut-off a priori and demonstrate it in a significant proportion of patients. Care must be taken to sample adequately the mucosa, and a process to ensure adequate sampling must be defined. UC in remission shows one of the following patterns: (1) chronic inflammation in the lamina propria with regular or irregular (including atrophic or shortened) glands; (2) lack of inflammation with either an atrophic glandular pattern with short crypts (which do not reach the muscularis mucosae), glands with lateral buddings, or dichotomic glands or an apparently normal glandular pattern (histologically normal mucosa).[96] Histologic assessment of disease activity may also be important for predicting relapse, and these include features of "persistent active inflammation" (polymorphonuclear leukocytes in the epithelium such as crypt abscesses) and basal plasmacytosis. Although not yet extensively studied, a 2-fold increase in relapse was observed in 2 trials in patients with persisting active inflammation.[57,62] These data were not confirmed in a more recent study that identified basal plasmacytosis as an independent predictor of relapse.[97]

The authors do not recommend that histologic remission be used as the primary end point for a therapeutic trial in patients with UC. Nevertheless, histologic remission and response are of interest and should be strongly considered as secondary end points in clinical trials, particularly when evaluating agents with novel mechanisms of action. Even when used as a secondary end point, consistency in the process of biopsy taking is important. In general, biopsy samples should be taken in the most severely affected area. If ulcers are present, they should be taken at the edge of those ulcers.

Quality of Life

The measurement of quality of life in clinical trials in patients with UC has been limited to date.[25,40,98] The instruments used to measure quality of life include the SF-36 and the IBDQ. In Crohn's disease, the end points based on the IBDQ for quality of life response and normal quality of life (consistent with clinical remission) in individual patients are a change of 16 points and an absolute score of 170 points, respectively.[37] Measurement of quality of life should always be performed in clinical trials in patients with UC and should be assessed both as the proportion of patients with improved quality of life and the proportion of patients with normal quality of life. Reporting the mean or median increase in quality-of-life scores in a population of patients is not acceptable as the sole measure of quality-of-life improvement but may be done as a secondary end point in conjunction with the determination of improved quality of life and normal quality of life. The authors recommend that the IBDQ and the SF-36 be routinely used as a secondary outcome measure in prospective random-

Table 5. End Points for Endoscopic Response to Induction Treatment for Mildly to Moderately Active Ulcerative Colitis

Author (reference)	Drug	Disease activity	Entry criteria	Instrument and end point	Placebo rate
Truelove[4]	Cortisone (oral)	Mild to severe	More than very mild symptoms	Endoscopic remission[a] Endoscopic improvement[b] at 6 weeks	11% 32%
Truelove[108]	Hydrocortiosone (enema)	Mild to moderate	Active symptoms, confirmed by endoscopy	Endoscopic improvement (defined as definite improvement) at 1 week	10%
Hanauer[21]	Budesonide (enema)	Mild to moderate	At least one of frequency and urgency of stools, diarrhea, or grossly visible blood, confirmed by sigmoidoscopic inflammation grade score ≥2	Sigmoidoscopic Inflammation Grade Score	−0.45 Significant reduction from baseline in mean score at 6 weeks
Baron[109]	Sulfasalazine	Mild to moderate	Typical symptoms, confirmed by endoscopy	Baron Index Endoscopic remission[c] Endoscopic improvement[d] at 3 weeks	5% 40%
Sutherland[30]	Mesalamine (enema)-Rowasa Enema	Mild to moderate distal colitis	Sutherland Index score ≥3, confirmed by endoscopy	Sutherland Index Significant reduction from baseline in mean Mucosal Appearance Index subscore of the Sutherland Index at 6 weeks	−0.97 points
Williams[110]	Mesalamine (suppository)-Rowasa Suppository-Trial 1	Mild to moderate ulcerative proctitis	Sutherland Index score ≥3, confirmed by endoscopy	Sutherland Index Endoscopic remission[e] at 6 weeks	25%
Williams[110]	Mesalamine (suppository)-Rowasa Suppository-Trial 2	Mild to moderate ulcerative proctitis	Sutherland Index score ≥3, confirmed by endoscopy	Sutherland Index Endoscopic remission[e] at 6 weeks	10%
Schroeder[26]	Mesalamine (oral)-Asacol	Mild to moderate ulcerative colitis	Not stated	Mayo Score Endoscopic remission[f] at 6 weeks	5%
Sninsky[31]	Mesalamine (oral)-Asacol	Mild to moderate ulcerative colitis	Active signs and symptoms	Mayo Score Endoscopic remission[g] at 6 weeks	5%
Rachmilewitz[10]	Mesalamine (oral)-Claversal Sulfasalazine	Mild to moderate ulcerative colitis	Clinical Activity Index Score ≥6, Endoscopic Index Score ≥4	Endoscopic Index Significant reduction from baseline in mean score Endoscopic remission[h] at 8 weeks	No placebo group
Hanauer[17]	Mesalamine (oral)-Pentasa	Mild to moderate ulcerative colitis	Clinical symptoms, Sigmoidoscopic Index Score ≥ 5	Sigmoidoscopic Index Significant reduction from baseline in mean score Endoscopic remission[i] at 8 weeks	−2.5 points 31%
Lichtenstein[41]	Mesalamine (oral)-SDP476	Mild to moderate ulcerative colitis	Sutherland Index score 4−10	Sutherland Index Endoscopic improvement[j]	37%
Kamm[42]	Mesalamine (oral)-SDP476	Mild to moderate ulcerative colitis	Sutherland Index score 4−10	Sutherland Index Endoscopic improvement[i] Endoscopic remission[j] at 8 weeks	42% 19%
Kruis[71]	Mesalamine (oral)-Salofalk Pellets	Mild to moderate ulcerative colitis	Clinical Activity Index Score 6−12, Endoscopic Index Score ≥4	Endoscopic Index Endoscopic improvement[k] Endoscopic remission[l] at 8 weeks	No placebo group
Van Assche[36]	Daclizumab-Zenepax	Moderate ulcerative colitis	Mayo Score 5−10	Mayo Score Endoscopic response[m]	51%
Feagan[25]	Anti-α4β7 integrin antibody-MLN-02	Moderate ulcerative colitis	Ulcerative colitis clinical score 5−9, stool frequency or rectal bleeding subscore ≥1, modified Baron sigmoidoscopy score ≥2	Baron Index Endoscopic response[n] Endoscopic remission[o] at 6 weeks	16% 8%
Rutgeerts and Sandborn ACT 1[29]	Infliximab-Remicade	Moderate to severe ulcerative colitis	Mayo Score 6−12, endoscopy subscore ≥2	Mayo Score Endoscopic response (mucosal healing)[p] at 8 weeks	34%
Rutgeerts and Sandborn ACT 2[29]	Infliximab-Remicade	Moderate to severe ulcerative colitis	Mayo Score 6−12, endoscopy subscore ≥2	Mayo Score Endoscopic response (mucosal healing)[p] at 8 weeks	31%
Tilg[116]	Pegylated interferon α	Mild to moderate ulcerative colitis	Clinical Activity Index Score >6 despite prednisone 10−40 mg daily	Endoscopic Index Endoscopic remission[l]	25%

[a]Endoscopic remission was defined as normal or near normal (slight hyperemia or granularity) sigmoidoscopic appearance.
[b]Endoscopic response defined as improved sigmoidoscopic appearance or endoscopic remission. All other patients classified as no change or worse.
[c]Sigmoidoscopic appearance classified as normal, inactive, moderately active, or active. Endoscopic remission was defined as normal or inactive sigmoidoscopic appearance.
[d]Endoscopic response defined as improved but still moderately active or endoscopic remission. All other patients classified as no change.
[e]Endoscopic remission defined as a Mucosal Appearance Index subscore of the Sutherland Index = 0 points.
[f]Endoscopic remission defined as a Findings of Flexible Proctosigmoidoscopy subscore of the Mayo Score = 0 points.
[g]Endoscopic remission defined as an Endoscopic Index score <4 points.
[h]Endoscopic remission defined as a Sigmoidoscopic Index score ≤4 points.
[i]Endoscopic improvement defined as a decrease from baseline in the Mucosal Appearance Index subscore of the Sutherland Index ≥1 point.
[j]Endoscopic remission defined as a Mucosal Appearance Index subscore of the Sutherland Index = 0 points.
[k]Endoscopic improvement defined as a decrease from baseline in the Sigmoidoscopic Index score ≥1 point.
[l]Endoscopic remission defined as a Sigmoidoscopic Index score <4 points.
[m]Endoscopic response defined as decrease from baseline in the Findings of the Flexible Proctosigmoidoscopy subscore of the Mayo Score ≥1 point.
[n]Endoscopic response defined as a modified Baron Score of 0 or 1 point.
[o]Endoscopic remission defined as a decrease from baseline in the modified Baron Score ≥2 points.
[p]Endoscopic response (mucosal healing) clinical remission defined as an absolute score on the Findings of the Flexible Proctosigmoidoscopy subscore of the Mayo Score ≤1 point.

Table 6. End Points for Histologic Response to Treatment and Induction of Remission for Mildly to Moderately Active Ulcerative Colitis

Author (reference)	Drug	Disease activity	Entry criteria	Instrument and end point	Placebo rate
Truelove[108]	Hydrocortisone (enema)	Mild to moderate distal colitis	Active symptoms confirmed by endoscopy	Histologic remission[a] at 1 week	0%
Hanauer[21]	Budesonide (enema)-Entocort Enema	Mild to moderate distal colitis	At least one of frequency and urgency of stools, diarrhea, or grossly visible blood, confirmed by sigmoidoscopic inflammation grade score ≥2	Decrease from baseline in Histopathology Evaluation Inflammation Grade[b] at 6 weeks	−0.45 points
Hanauer[17]	Mesalamine (oral)-Pentasa	Mild to moderate ulcerative colitis	Clinical symptoms, Sigmoidoscopic Index Score ≥5	Decrease from baseline in Histologic activity[c] at 8 weeks	−37%
Kruis[71]	Mesalamine (oral)-Salofalk Pellets	Mild to moderate ulcerative colitis	Clinical Activity Index Score 6−12, Endoscopic Index Score ≥4	Histology improvement[d] at 8 weeks	No placebo group
Pullan[152]	Nicotine (transdermal)	Mild to moderate ulcerative colitis	Active ulcerative colitis	Decrease from baseline in the Truelove and Richards acute inflammatory activity subscore[a] at 6 weeks	−0.0 points
Sandborn[33]	Cyclosporine (enema)	Mild to moderate ulcerative colitis	Active ulcerative colitis	Histologic improvement[e] Histologic remission[f] at 4 weeks	35% 5%
Sinha[114]	Epidermal growth factor (enema)	Mild to moderate ulcerative colitis	Powell-Tuck Index score ≥5.	Decrease from baseline in the Histologic Score[g] at 2 weeks	−0.5 points
Sandborn[35]	Repifermin	Mild to moderate ulcerative colitis	Mayo Score 3−10	Decrease from baseline in Histopathology Evaluation Inflammation Grade[b] at 4 weeks	−0.4 points
Van Assche[36]	Daclizumab-Zenepax	Moderate ulcerative colitis	Mayo Score 5−10	Geboes Index Decrease from baseline in the Geboes Index[h] at 8 weeks	−0.6 points
Feagan[25]	Anti-α4β7 integrin antibody-MLN-02	Moderate ulcerative colitis	Ulcerative colitis clinical score 5−9, stool frequency or rectal bleeding subscore ≥1, modified Baron sigmoidoscopy score ≥2	Riley Score Decrease from baseline in the modified Riley Score[i] at 6 weeks	−0.9 points

[a]Histologic inflammation was classified according to the Truelove and Richards score into 4 grades: 1, no significant inflammation; 2, mild inflammation; 3, moderate inflammation; 4, severe inflammation.[56,57] Remission was defined as no significant inflammation.
[b]Histopathology Evaluation Inflammation Grade measured according to 3 domains: 1, active inflammation (graded 0−3); 2, chronic inflammation (graded 0−2); 3, crypt distortion (graded 0-3).[21] Histologic activity measured as a decrease from baseline in the mean total inflammation grade.
[c]Histologic activity graded on a 4-point categorical scale: normal colonic mucosa = 0 through 3 = high grade, active inflammatory bowel disease.[17] Histologic activity measured as a decrease from baseline in the histologic activity grade.
[d]Histology improvement was measured using the Riley score (histology activity ranges from 0 to 4 points).[62]
[e]Histologic activity graded on a 4-point Histologic Disease Activity Index.[33] Histologic improvement defined as a decrease from baseline in the Histologic Disease Activity Index ≥1 point.
[f]Histologic remission defined as a Histologic Disease Activity Index[33] score = 0 points.
[g]Histologic activity graded on a 4-point (0−3) histologic score.[6]
[h]Histologic activity graded using the Geboes Index (see Supplementary Table 15 online at www.gastrojournal.org), an instrument with 6 domains (structural [architectural change], chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction, and erosions or ulceration).[64] Scores can range from 0 to 5.4, with higher scores indicating more severe histologic inflammation.
[i]Histology improvement was measured using a modification of the acute inflammation subscore of the Riley Score (acute histologic inflammation activity ranges from 0 to 7 points).[62]

ized controlled trials to ensure that quality of life is improved in medically treated patients with UC.

Noninferiority Study Designs

Because mesalamine is safe and effective for the induction and maintenance of response and remission in patients with UC, true placebo-controlled trials in which no concomitant therapies for UC are permitted may not always be possible. Thus, to evaluate new therapies as potential first-line treatments (as an alternative to mesalamine), noninferiority (equivalence) study designs may be required.[99,100] Few noninferiority studies have been performed in patients with inflammatory bowel disease.[69,101,102] A recent systematic review reported that a majority of "equivalency" studies in digestive disease trials are actually failed superiority studies rather than properly designed and powered noninferiority trials.[103] The majority of superiority clinical trials in patients with UC are powered to detect differences ("superiority margin") of 15%–20%. Differences of this magnitude have generally been considered clinically meaningful. The "noninferiority margin" for an equivalence trial should be approximately 50% of a superiority margin that would be considered clinically meaningful. Thus, the noninferiority margin in clinical trials in patients with UC is approximately 10% (ie, the upper boundary of the 95% confidence interval of the difference in remission rates between the 2 therapies cannot exceed 10%). An alternative approach is to use a value for the noninferiority margin that is lower than the lower boundary of the 95% 2-sided confidence interval for the pooled data for the comparator therapy (thus taking into account the variability of treatment differences across studies).[104] Recent discussions with regulatory authorities suggest that a noninferiority margin of approximately 10% would be required to gain regulatory approval for a therapy for UC

on the basis of noninferiority to mesalamine, although 15% has been accepted in some jurisdictions.

Placebo Response

When designing placebo-controlled trials in patients with UC, careful consideration must be given to the expected placebo response for the specific treatment indication and patient population and taking into account the primary end point of the study and the instrument used to measure disease activity. Three metaanalyses have been performed that quantify the placebo response in patients with UC.[105–107] These metaanalyses as well as the placebo response and remission rates outlined in Tables 1–6 should be used to estimate the expected placebo remission rate to perform power calculations when designing placebo controlled trials.

Conclusions

During the last 50 years, there has been considerable heterogeneity and confusion regarding the optimal instruments (activity indices) and end points for assessing the efficacy of medical therapies for UC. This review has allowed the development of a consensus opinion regarding the optimal end points for the indications of treatment and induction of remission, maintenance of remission, and endoscopic remission in UC patients. There is preliminary experience with clinical trials targeting the indications of corticosteroid sparing, but determination of the optimal end point for clinical trials for this indication is still in evolution. The definition of histologic improvement or remission and the application of these end points in clinical trials have not yet been applied. Likewise, the application of quality-of-life improvement or remission has only recently been undertaken in a small number of clinical trials. Examination of the relevance of various definitions of response and remission by the academic investigators, the pharmaceutical industry, and the regulators is an important issue that should be examined collaboratively. An "optimal" scoring instrument for UC is still to be developed and will require validation before extensive use in clinical trials can be promoted.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1053/j.gastro.2006.12.038.

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