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Implementing the Concept of Continuous Clinical Response Into Clinical Practice for Ulcerative Colitis

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BACKGROUND & AIMS: **Ulcerative colitis (UC) is a complex and progressive disease that has a significant humanistic and economic impact in patients and the wider society. Disease control is still an unmet need for a large proportion of patients. The aim of this article was to review the current evidence to assess the feasibility, value, and impact of integrating continuous clinical response (CCR) as a patient-reported outcome into routine management of UC.**

METHODS: **Literature searches in PubMed, Google Scholar, and conference proceedings were undertaken to retrieve the relevant articles regarding burden and course of disease, outcome measures in UC, tools for measuring disease activity, and models for patient's self-monitoring.**

RESULTS: **The concept of CCR was first introduced during the PURSUIT-M trial, where evidence was provided to support the clinical and quality of life benefits of achieving CCR. However, patient monitoring as implemented during the trial was not feasible for its use in the real world. Thus, a simple self-reported score (eg, PRO2) to monitor CCR, with good correlation with more complex procedure-driven indices, was identified for its use in routine patient care. Feasibility of introducing this easy-to-use tool over time as an integral part of patient management was also explored.**

CONCLUSIONS: **The introduction of CCR as a management goal for UC patients may pose the step change needed to improve disease course and patient's life. Providing patients with simple tools to continuously monitor their disease activity is the first step for an integrated self-monitoring model of care in UC.**

Keywords: Disease Activity; Self-monitoring; Golimumab; PURSUIT.

Ulcerative colitis (UC) is a chronic inflammatory and disabling disorder of the large bowel that creates a substantial clinical and economic burden. UC course often requires long-term therapy with multiple medications, resulting in a high burden of disease and decreased health-related quality of life.[1,2]

A recent multicenter European study (UC CARES) of patients diagnosed with moderate to severe UC (Mayo score $\geq$6) who were managed with conventional therapy in 11 European countries showed a low proportion of patients (12.8%) who were in corticosteroid-free remission in the last 2 months (ie, controlled) versus the majority of patients (87.2%) who were classified as non-controlled.[3] The UC CARES cross-sectional study collected baseline disease characteristics from 250 consecutive UC patients, and approximately 76 of these patients (30%) were seen at unscheduled visits, demonstrating the irregular pattern of difficult-to-control symptoms in UC. In addition, a total of 48% of UC patients were reported to be dissatisfied with their current treatment.[4] Thus, disease control in clinical practice is still an unmet need for many patients with UC because of disease-related symptoms and the impact on their lives.

Abbreviations used in this paper: **CCR, continuous clinical response; CRP, C-reactive protein; IBD, inflammatory bowel disease; IBDQ, inflammatory bowel disease questionnaire; PGA, physician global assessment; PROMIS, Patient Reported Outcomes Measurement Information System; Q4W, every four weeks; QoL, quality of life; SCCAI, simple clinical colitis activity index; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis.**

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In spite of this, moderately active UC is too often perceived as a benign disease, which may result in patients not being adequately treated and physicians delaying more effective treatment until later in the disease course by first allowing patients to receive multiple cycles of steroids and immunomodulators. Moreover, uncontrolled inflammation results in bowel damage,[5,6] which in turn may result in colectomy and increased colorectal cancer risk.[7,8] It is also important to note that colectomy does not represent a cure for UC but only a decent therapeutic option. If there are any surgical complications, these may also represent a substantial burden in terms of cost and quality of life (QoL).[9]

The concepts of durable sustained response and continuous clinical response (CCR) have recently emerged in Crohn's disease[10] and UC,[11] respectively. Specifically, CCR was introduced as a primary end point in the PURSUIT maintenance trial (PURSUIT-M) of biologic-naive UC patients with moderate to severe disease activity responding to golimumab induction treatment at week 6 during PURSUIT subcutaneous or PURSUIT intravenous induction trials (PURSUIT-SC, PURSUIT-IV).[11] CCR was defined as a sustained clinical response without treatment failure through 54 weeks, assessed by partial Mayo score every 4 weeks (Q4W) and full Mayo score at weeks 30 and 54. CCR patients are thus in a state of continuous response without loss of response from week 6 through week 54. Furthermore, golimumab dose increase, new use or change of prohibited concomitant medication, and surgery were considered treatment failure and loss of CCR state. This outcome may be the best way to change disease course and patient's life, because it incorporates the notion of continuous monitoring of patient's outcomes targeting continuous control of disease severity.

However, to introduce CCR as an important goal of UC patient management in routine clinical practice, there is the need for a simple self-reported tool that patients can use themselves to assess their clinical response over time without depending on scores that require endoscopic evaluation or physician assessment. Hence, the overall aim of this article was to determine the feasibility and value of integrating CCR as a patient-reported outcome into routine management of UC, as well as to elucidate the impact this may have for patients and physicians in clinical practice.

Need for Achieving Continuous Clinical Response: Lessons From the PURSUIT Maintenance Trial

The measurement of clinical response as the primary end point in clinical trials evaluating the efficacy of different biologics in patients with UC has so far mainly been done at a single time point (ie, at landmark end points), for example at week 8, week 10, or week 52.[12–14]

Some early trials have attempted to quantify response to treatment over time (sustained), when presenting the results on remission at both week 30 and week 54.[15] A recent UC study investigating the efficacy and safety of adalimumab in routine clinical practice included the measurement of sustained response at weeks 12, 30, and 52 as a primary end point.[16] However, in this study, the definition of maintained response through week 52 without intermediate relapse differed from the original CCR definition established during the PURSUIT-M trial. In addition, sustained clinical response (defined as persistent steroid-free clinical improvement [ie, absence of diarrhea and blood] during a 12-month follow-up period) was a pre-specified outcome measure in a retrospective observational study.[17] In this case, the outcome measure used did not meet the criteria of the CCR definition either.

It was during the PURSUIT-M trial that the concept of CCR was introduced.[11] This trial was carried out to assess the efficacy and safety of 50-mg and 100-mg subcutaneous anti–tumor necrosis factor antibody golimumab administered Q4W as maintenance regimen compared with placebo treatment (ie, withdrawal of golimumab after response to induction) in biologic-naive mild to moderate UC patients. The primary end point of PURSUIT-M trial was CCR as defined above.[18]

Findings from the PURSUIT-M clinical trial provided evidence to support the clinical and QoL benefits associated with CCR (Table 1). A total of 26.6%, 41.7%, and 42.4% of placebo and golimumab 50 mg and 100 mg, respectively, achieved endoscopic healing (endoscopic subscore 0/1) at weeks 30 and 54 of the trial, with both golimumab maintenance groups yielding significantly better results than golimumab withdrawal (placebo maintenance).[11] At week 54, patients with CCR showed endoscopic healing (score 0/1) in 90.4% (golimumab maintenance) and 87.5% (golimumab withdrawal), respectively, compared with 2.6% and 1.9% of the patients not in CCR (Table 1).[19] In addition, QoL was profoundly affected by the CCR versus non-CCR status of the UC patients in the PURSUIT-M trial. In the combined 50 and 100 mg golimumab maintenance group, 75% of patients in CCR reported normal QoL (inflammatory bowel disease questionnaire [IBDQ] score >170), whereas only 24.4% of patients without CCR exhibited normal QoL at week 54 (Table 1).[19]

Therefore, CCR can be considered as a good outcome measure from both patient's and physician's perspective. Gastroenterologists aim for their patients to be in clinical remission, which in turn reassures them that their therapeutic approach is effective and adding to the patient's QoL. CCR (vs non-CCR) is also associated with other important clinical treatment goals of UC, including remission (67.1% vs 1.9%) and being off steroids in patients taking steroids at baseline (75.3% vs 4.6%) after 54 weeks of golimumab maintenance therapy.[19] This is also of interest from a payer perspective, because well-controlled, well-monitored patients generate lower healthcare expenditures related to UC.[20]

Table 1. Clinical Outcomes Based on CCR at Week 54 in the PURSUIT-M Study[11]

Clinical end points	Non-CCR		CCR	
	Golimumab withdrawal	Golimumab maintenance[a]	Golimumab withdrawal	Golimumab maintenance[a]
Corticosteroid use				
Randomized patients receiving concomitant steroids at week 0 (n)	60	87	27	73
Patients not receiving corticosteroids at week 54 (%)	1.7	4.6	66.7	75.3
Remission				
Randomized patients (n)	106	156	48	146
Patients in clinical remission[b] at week 54 (%)	0.9	1.9	68.8	67.1
Endoscopic healing				
Randomized patients (n)	106	156	48	146
Patients with endoscopic healing at week 54 (%)	1.9	2.6	87.5	90.4
IBDQ score				
Randomized patients (n)	105	156	48	144
Change from week 0 through week 54 [mean (standard deviation)]	−38.9 (32.1)	−36.9 (37.6)	10.6 (18.2)	11.3 (28.1)
Patients with IBDQ score >170 at week 54 (%)	18.1	24.4	81.2	75.0

[a]Combined 50 mg and 100 mg golimumab maintenance.
[b]Clinical remission was defined as Mayo score ≤2 points, with no individual subscore >1, and mucosal healing was defined as Mayo endoscopy subscore of 0 or 1.

Hence, introduction of CCR as an important goal of patient management in routine clinical practice would be beneficial. However, CCR as implemented in the PURSUIT clinical trial required patients to attend 4-weekly clinic visits, which would result in an unnecessary burden for patients and additional healthcare cost in the real-world UC setting. There is a need for defining the use of a simple self-reported tool that patients can use to assess their clinical response over time.

What Measures Are Currently Available to Assess Patient Outcomes in Ulcerative Colitis?

There is a broad range of measures available of various degrees of complexity to evaluate disease activity in UC patients (Table 2). Requirements for physician assessment, physical examination, laboratory investigation, or even more invasive procedures such as endoscopy differ among the various scores/indices. The added value of the information derived from endoscopic findings in evaluating UC activity after diagnosis is not clear, when compared with scores that are based on noninvasive procedures only.[21] Likewise, a score requiring laboratory blood parameters may not be practical to quickly assess outcomes because of the time lag from analysis to results.[22] On this basis, simpler scores have been created to overcome some of the limitations of more complex procedure-dependent indices and enable quicker patient self-assessment of disease activity.

The Simple Clinical Colitis Activity Index (SCCAI) with patient-reported symptom scores only has proven useful for initial assessment of disease activity and relapse,[22,23] and it was well-correlated with more complex scores requiring invasive procedures such as the Powell-Tuck Index or the Seo index.[22]

The partial Mayo score and a 6-point Mayo scale were also developed to facilitate assessment of disease severity and increase patient willingness to undertake such evaluations in trials. Both were derived from the full Mayo score (Table 2); in the case of the partial Mayo, the endoscopic component of the full Mayo score was excluded, whereas in the 6-point scale only the stool frequency and rectal bleeding components were maintained (Supplementary Material). Both measures have been found to perform as well as the full Mayo score,[24] but with the advantage of being simpler because they do not include information that is based on invasive procedures. However, the partial Mayo score includes information that is based on physician rating of disease activity (physician global assessment [PGA]); thus it cannot be used as a patient self-reported measure.

The 6-point scale (stool frequency and rectal bleeding score combined) may be more suitable for this purpose. Reinisch et al[25] characterized the association of the partial Mayo score components of stool frequency, rectal bleeding, and their combination (6-point scale, also called PRO2) with CCR in the PURSUIT-M trial with golimumab. CCR was found to be equally associated with partial Mayo score, PRO2, and Mayo endoscopy score at weeks 30 and 54 without difference of the area under the receiver operating curve.[25] This implies that frequent patient self-monitoring of PRO2 may be a useful surrogate of endoscopy. However, controlled trials comparing these 2 strategies (treatment that is based on symptoms versus treatment to achieve mucosal healing) are eagerly awaited.

Lewis et al[24] previously found similar results in a study using clinical trial data from UC patients. The partial Mayo score and the simpler 6-point scale (PRO2) performed as

Table 2. Measures to Evaluate Disease Activity in Patients With UC

Measure	Criteria assessed	Evaluation requirements
Truelove and Witts Severity Index[43]	Temperature Pulse rate Hemoglobin Erythrocyte sedimentation rate Bowel frequency	Physician assessment, laboratory investigations, and patient self-reported information
Complex Integrated Disease Activity Index or Seo Index[44]	Bloody stool Bowel movements Erythrocyte sedimentation rate Hemoglobin Serum albumin	Physician assessment, laboratory investigations, and patient self-reported information
Powell Tuck Index[45]	Bowel frequency Stool consistency Abdominal pain Anorexia Nausea/vomiting General health Extracolonic manifestations Abdominal tenderness Body temperature Blood in stool Sigmoidoscopy	Physician assessment, invasive procedures, and patient self-reported information
SCCAI[22]	Bowel frequency (day and night) Urgency of defecation Blood in stool General well-being Extracolonic features	Patient self-reported information
Mayo Score[46]	Stool frequency Rectal bleeding Endoscopic findings PGA of disease activity	Physician assessment, invasive procedures, and patient self-reported information
Partial Mayo Score[24]	Stool frequency Rectal bleeding PGA	Physician assessment and patient self-reported information
6-point scale, PRO2[24]	Stool frequency Rectal bleeding	Patient self-reported information

well as the full Mayo score when assessing clinical response as perceived by the patient. Jairath et al[26] also supported the use of patient-reported outcomes (PRO2) and endoscopy as co-primary end points in UC trials.

In addition, recommendations on evidence-based treatment targets for inflammatory bowel disease (IBD) have been recently issued as part of the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program, where a group of 28 international specialists agreed that the target for UC should be clinical/PRO remission (ie, resolution of altered bowel activity and rectal bleeding) and endoscopic remission.[27] Thus, PRO2 may be used to monitor patients' UC symptoms remotely and may provide a useful measure to assess for CCR in daily clinical practice.

The Patient Reported Outcomes Measurement Information System (PROMIS) initiative of the National Institutes of Health has also been implemented and validated in patients with gastrointestinal diseases (including IBD) as a set of patient-reported outcomes that cover physical, mental, and social health.[28,29] Associations between the health status and functioning measured by PROMIS and other self-reported disease activity scores have been found. Better PROMIS scores have also been associated with improvement in disease activity.[28]

However, it is also important to note certain limitations that may be inherent to the use of self-administered tools. The degree of patient's compliance and adherence to self-monitoring may be variable because of various reasons such as self-awareness about the severity of the disease, education, time available for regular monitoring, and other patient factors. The patient can potentially underestimate the role of the doctor, which may damage the patient-doctor relationship, with physicians feeling a loss of control in the management of their patients.[30] Therefore, it is important that the physician is involved in the (remote) self-monitoring of disease activity, and that a multidisciplinary management, including patient education to enhance adherence, is offered together with other professionals (eg, IBD nurses). This is where PRO2 holds an advantage, because the reported answers are observations that are not likely to be affected by patient's perceptions and knowledge.

Mayo score has been the preferred outcome measure in randomized trials but not in real-world practice.

Partial Mayo and PRO2 perform equally well.[24,25] Because PGA is subjective and is not a PRO according to the Food and Drug Administration, STRIDE[27] recommended PRO2 (stool frequency plus rectal bleeding score of partial Mayo score) and endoscopy for monitoring of UC disease activity. This aligns with the Food and Drug Administration's plan to move to patient-reported outcomes and endoscopy as co-primary end points of future UC randomized trials. This approach was tested by Jairath et al[26] in a post hoc analysis of the mesalazine (mesalamine) induction trial results in UC. The authors concluded that PRO2 and endoscopy are qualified co-primary end points to assess disease activity.

How Can We Implement an Integrated Self-monitoring Model to Assess Continuous Clinical Response in the Real World?

Patients increasingly seek to take part in management and therapeutic decisions according to their preferences on medication and follow-up, which in turn can have an effect on their reported QoL and ultimately on long-term adherence and resource optimization. Empowering patients to actively participate in their management and assess their clinical outcomes may contribute to a better understanding of the disease, its control, and self-perception. Healthcare authorities and other key stakeholders are also willing to introduce programs and tools integrating patient self-monitoring as well as addressing gaps in current care and creating new models, aiming to personalize care, reduce healthcare resources, and improve patient's QoL.[31]

It has been previously recognized that patients with long-term chronic conditions such as UC would benefit from learning self-monitoring and having an integrated network of care. This should also include patient's education and timely communication with healthcare professionals when required.[31] A randomized controlled study of 263 IBD patients, where 133 patients received education by dedicated staff and 130 patients did not, showed a significant improvement in the skills of educated IBD patients (as measured by the ECIPE score variation within each group), thus supporting the benefits of educational programs in patient's lives.[32] Benefits from self-monitoring, such as improved QoL or reduction of healthcare resource use, have already been reported for pediatric IBD[33] and other disease areas such as asthma, congestive heart failure, and chronic obstructive pulmonary disease.[34–37] Patients and physicians integrating self-monitoring into their healthcare model should ensure the establishment of a collaborative partnership between them, avoiding any damage to the doctor-patient relationship.[30]

Thus, the need for easy-to-use and reliable tools to facilitate self-monitoring of UC patients is clear to achieve a better patient care model. Figure 1 outlines a proposal for an integrated self-monitoring model to assess CCR in the real world. The use of simple indices to evaluate disease activity and their correlation to more complex measures in predicting patient's prognosis have been previously described in this article. The ability to introduce such tools, for example the PRO2 or SCCAI, as an important part of patient self-monitoring to evaluate the patient-reported CCR over time in the real world can be empowering. Remote monitoring of symptoms can facilitate patient's own monitoring, reduce frequency of clinic visits, target specialized care when most needed, and optimize patient-physician interactions. A Spanish study of 199 patients showed a substantial degree of agreement for most domains between the SCCAI scores reported by patients at home (by using an online tool) and those obtained from assessments of physicians in their clinics (kappa above 0.60 in all domains except urgency of defecation and arthritis, where kappa was 0.57 and 0.58,

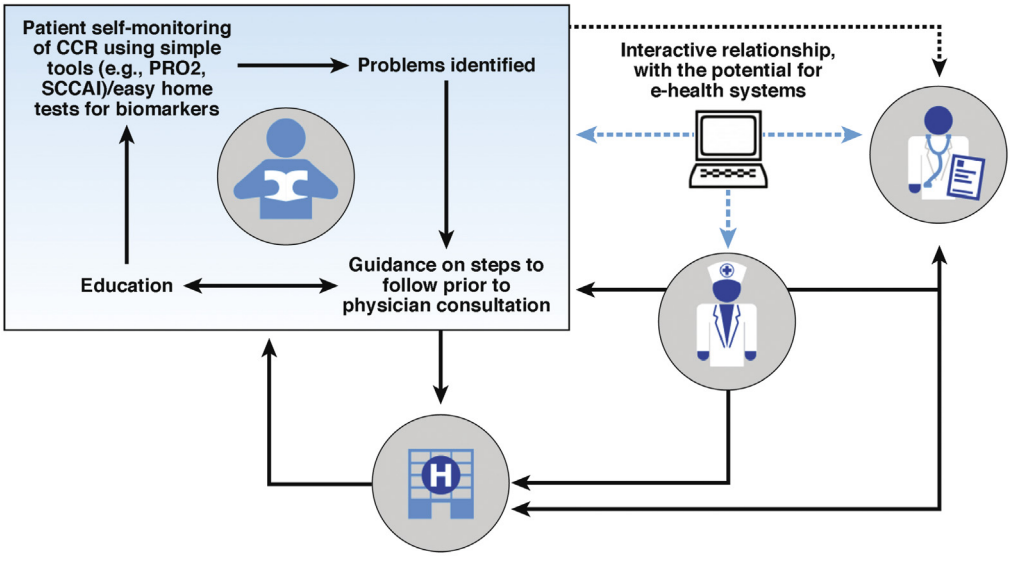

Figure 1. Proposed integrated self-monitoring model to assess CCR in the real world.

respectively).[38] These results support the idea that remote self-monitoring of UC patients with a simple tool may be possible for patients with controlled disease and can potentially reduce the number of scheduled visits to the clinic. However, prompt and easy access needs to be provided in case of uncontrolled disease and UC flare.

In addition, there is the potential for predictive and prognostic biomarkers to be integrated in this remote management model through easy home tests. Reinisch et al[39] showed that fecal calprotectin at week 6 could predict CCR in patients with moderate to severe UC who responded to golimumab induction at week 6 as part of the PURSUIT-M trial. Elkjaer et al[40] also described fecal calprotectin home testing as a reliable alternative to laboratory tests with enzyme-linked immunosorbent assay technique, showing a sensitivity of 97.2% and a specificity of 88% with high predictive values. A Danish study reported reduced number of scheduled visits (74 versus 172 outpatient visits) in pediatric patients with IBD by using calprotectin and remote self-monitoring when compared with a control group.[33] It is well-known that C-reactive protein (CRP) is elevated only in severe forms of UC and that it should not be a treatment target in UC patients.[39] Consistently in the PURSUIT trial, the change of CRP from start (week 0 of induction) to week 6 (end of induction), CRP at week 6 (end of induction), and normalized CRP at week 6 (<8.0 mg/L) were not predictors of CCR (sustained response through week 54 without treatment failure).

The use of innovative management tools (eg, via applications, websites, etc) can allow for an interactive relationship between patients and physicians where both contribute to real-time disease monitoring (Figure 1). Several of these tools have already become available in the last few years and aim at facilitating the management of UC patients. Some authors have evaluated the use of these new approaches (eg, use of specific web applications or integral eHealth systems) to assess their advantages in patient management versus regular care. A recent randomized controlled trial conducted in Denmark and Ireland evaluated the use of an eHealth treatment program versus regular care in 333 adult patients with mild/moderate UC and 5-aminosalicylate acid treatment during 1 year. Patients allocated to the eHealth treatment program arm were asked to connect to a specifically developed web system monthly during follow-up period and more regularly (daily/weekly) during relapse. The tool helped them to identify relapses and guided them to start the correct treatment or to consult the physician in case of alarm symptoms (ie, more than 6 stools/day, daily rectal bleeding [with every bowel movement], rectal bleeding occurring between relapses, fever >37.5°C, heart rate >90 per minute, severe abdominal pain and/or tenderness, symptoms persisting for more than 11 days despite intensified treatment, and unexplained weight loss). The new system was preferred by the vast majority of the web patients, and improvement versus regular care was observed in (1) adherence rates (adherence to 4 weeks of acute treatment increased by up to 44% in web patients); (2) IBD knowledge (76% of eHealth patients showed an improved understanding of their disease versus 39% of patients on regular care); (3) relapse duration (median duration decreased from 77 days in the control group to 18 days in the web patients); (4) outpatient clinic visits (number of visits decreased from 92 visits in regular patients to 35 visits in web patients, resulting in savings of 189 Euros per patient per year); and (5) QoL (improvements in Danish web patients versus control patients in disease-specific QoL, $P = .04$; general health, $P = .009$; vitality, $P = .03$; role emotional, $P < .0001$; and social functioning, $P = .002$).[41,42]

There is a need for a multidisciplinary approach while implementing this new concept of (more frequently) remote monitoring and reporting PRO2 to the IBD clinic. In such system, the IBD nurse could be the gatekeeper and reviewer of incoming PRO2 data. No expensive technology is required, and a web-based platform or smart phone application can be used for remote reporting of PRO2. Several eHealth smart phone applications are already available in other diseases, and others are currently tested in IBD. However, the cost-effectiveness of this new approach as well as the potential increased workload on providers will require additional investigation.

Thus, there is potential for the implementation of an integrated self-monitoring model to assess CCR in the real world, which would offer benefits for both patients and physicians, enabling an interactive and evolving management of UC. Such a model could also reduce healthcare costs for national healthcare services by enhancing tighter disease control.

Conclusions

Providing patients with the necessary infrastructure and tools to implement an easy self-monitoring system to achieve long-term disease control could result in important changes in patient's disease course, QoL, self-perception, and overall well-being. Integrating patient-reported CCR as part of the routine care of patients can be a step change in UC management by empowering patients and strengthening physicians' care models and their relationships with patients. Colectomy is not a cure for UC, and postoperative course is associated with high costs, ranging from $18,650/patient with complications at a 6-month follow-up to $34,714/patient with complications during a 5-year period.[9] Achieving CCR might be the only way to change disease course and patients' QoL and could lead to cost savings for the healthcare system. This will require further investigation in upcoming disease-modification trials.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.10.001.

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Conflicts of interest
Laurent Peyrin-Biroulet has received lecture fees from Merck, AbbVie, Janssen, Takeda, Ferring, Norgine, Tillots, Vifor, Therakos, Mitsubishi, and HAC-Pharma and consulting fees from Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, and Forward Pharma GmbH. Gert Van Assche has received research support from the University of Leuven, AbbVie, and MSD; speaker's fees from AbbVie, Ferring, MSD, and Janssen; and consulting fees from the University of Leuven, AbbVie, MSD, Ferring, UCB, and Takeda. Alessandro Armuzzi has been a consultant to AbbVie, Celltrion, Hospira, Ferring, Janssen, Lilly, MSD, Mundipharma, Pfizer, Samsung, Sofar, and Takeda; received lecture fees from AbbVie, AstraZeneca, Chiesi, Ferring, Hospira, Janssen, MSD, Mundipharma, Otsuka, Takeda, and Zambon; and received research grant from MSD. Laura Garcia-Alvarez is a consultant to Merck. Nuria Lara is a consultant to Merck. Christopher M. Black is a Merck stockholder and Merck employee. Ahmed Khalifa is a Merck stockholder and Merck employee. Freddy Cornillie is a Merck employee. Sumesh Kachroo is a Merck stockholder and Merck employee.

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Supplementary Material

Questions of the Partial Mayo Score[24]

Patient-reported symptoms.

a. Stool frequency (based on the past 3 days)
   - Normal number of stools (0)
   - 1–2 stools more than normal (1)
   - 3–4 stools more than normal (2)
   - 5 or more stools more than normal (3)

b. Rectal bleeding (based on past 3 days)
   - No blood seen (0)
   - Streaks of blood with stool less than half the time (1)
   - Obvious blood with stool most of the time (2)
   - Blood alone passed (3)

Physician-reported rating.

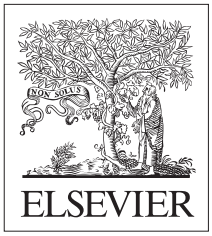
c. Physicianś global assessment
   - Normal [subscores are mostly 0] (0)
   - Mild disease [subscores are mostly 1] (1)
   - Moderate disease [subscores are mostly 1–2] (2)
   - Severe disease [subscores are mostly 2–3] (3)

The physician's global assessment acknowledges the subscores, the daily record of abdominal discomfort and functional assessment and other observations such as physical findings, and the patient's performance status.

Questions of the PRO2[24]

a. Stool frequency (based on the past 3 days)
   - Normal number of stools (0)
   - 1–2 stools more than normal (1)
   - 3–4 stools more than normal (2)
   - 5 or more stools more than normal (3)

b. Rectal bleeding (based on past 3 days)
   - No blood seen (0)
   - Streaks of blood with stool less than half the time (1)
   - Obvious blood with stool most of the time (2)
   - Blood alone passed (3)



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