

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Assessing Disease Activity in Patients with Ulcerative Colitis



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G&H What factors should clinicians consider when assessing disease activity in patients with ulcerative colitis?

AW/ST Clinicians need to consider 4 different factors when assessing ulcerative colitis (UC) disease activity: clinical symptoms, quality of life, endoscopy, and histology. First, clinicians should assess clinical parameters—rectal bleeding and stool frequency are routinely assessed in clinical practice, and experienced clinicians assess symptoms such as urgency, incontinence, and nocturnal diarrhea, even though these latter factors are rarely included in disease activity indices. These factors are significant because of their central importance to patients. Since inactive disease is associated with normal activity, another important indicator of disease activity is quality of life, which measures patients' ability to enjoy normal social, occupational, and sexual activities. Finally, disease activity can be assessed by endoscopy and histology. It is by considering all of these factors together that clinicians can best understand disease activity.

G&H How reliable are clinical symptoms as a measure of disease activity?

AW/ST Clinicians cannot rely on patient symptoms alone when making treatment decisions because clinical

symptoms often either underestimate or overestimate UC disease activity. For this reason, objective measures of disease activity are needed. This is not to advocate the use of a specific disease activity index, since all have flaws, but clinicians should use objective measures such as C-reactive protein (CRP), fecal calprotectin, or endoscopy to complement assessment of the patient's clinical symptoms.

G&H What is the rationale for continuing therapy if patients are asymptomatic?

AW/ST Among patients in clinical remission, persistent mucosal inflammation is associated with a higher risk of relapse. Studies of patients with UC have shown that mucosal appearance 8 weeks after starting treatment with infliximab (Remicade, Janssen Biotech) is associated with the likelihood of colectomy within the following 12 months. Similarly, among patients with UC who are in remission, 90% of treatment-adherent patients remain in remission, while only 39% of patients who are nonadherent to therapy remain in remission. Given these findings, treating symptoms alone is insufficient to achieve optimal long-term outcomes. Instead, clinicians should strive for mucosal healing, as this measure appears to predict long-term remission, and patients should be counseled about the importance of continuing therapy once in remission.

G&H How important is endoscopy for measuring disease severity?

AW/ST Endoscopy is frequently used in clinical practice both to confirm a patient's diagnosis and to assess disease severity. Indeed, given our current understanding that mucosal healing leads to better outcomes, including endoscopy as part of the patient's evaluation is appropriate. The trouble, of course, is that patients do not like to undergo endoscopy. Endoscopic assessment also plays a key role in measuring outcomes in clinical trials, since disease severity as measured by endoscopy is considered to be independent of the symptom score, especially if there is central reading of endoscopy videos.

To help standardize endoscopic assessment, a validated endoscopic scoring system called the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) has been developed. This system assesses disease severity using a combination of 3 endoscopic factors: vascular pattern, bleeding, and ulceration/erosion. For each of these factors, the endoscopist scores the patient, and these subsection scores are then summed to yield an overall score ranging from 0 to 8. The UCEIS score was found to account for 88% of the overall variance in observed endoscopic activity as measured on a visual analog scale. Prior to the development of this scoring system, different physicians often had very different (individual) definitions for mild, moderate, and severe UC. For example, a study conducted at the John Radcliffe Hospital in Oxford, in which 100 UC sigmoidoscopy videos were assessed by 4 different doctors, found only 20% agreement among physicians as to whether the patient's condition should be categorized as remission, mild disease, moderate disease, or severe disease. The goal of the UCEIS is to standardize how endoscopists score their findings.

G&H How well does endoscopy correlate with histology?

AW/ST Endoscopy and histology are complementary. In a study of 91 patients, researchers found 89% agreement between endoscopy and histopathology for identifying patients in remission. However, this percentage decreased significantly when physicians were asked to categorize disease as mild, moderate, or severe. Another finding of this study was that endoscopy and histology do not always correlate with symptoms: Among patients who were in remission according to both endoscopy and histology, one third still had clinical symptoms of disease activity. When the study assessed clinical symptoms, endoscopy, and histology, agreement was reduced to well below 50%.

One specific advantage of histology is that the lack of microscopic inflammation on mucosal biopsy effectively excludes active UC, and a biopsy sample can be assessed

independently from endoscopy. In the context of clinical trials, researchers have discussed whether to incorporate histology into study designs, as this addition would certainly decrease the subjectivity of the study results. However, including histology in a clinical trial makes the trial process more complex—as well as more time-consuming and expensive—since a central reader is needed to evaluate the histopathology.

G&H Are fecal biomarkers useful for measuring disease activity?

AW/ST Yes, fecal biomarkers are noninvasive surrogates for mucosal healing, and they are increasingly being used to assess disease activity. None are yet sufficiently specific to replace endoscopy, but they are a useful guide of disease activity in practice, if only for their negative predictive value (where a normal result effectively excludes inflammation). Neutrophil-derived proteins can potentially act as biomarkers of endoscopic inflammation. Specifically, patients with active UC have higher levels of fecal lactoferrin, calprotectin, or neutrophil elastase. While more research on fecal biomarkers is needed, studies have shown that a high fecal calprotectin in a patient with UC has a high negative predictive value for remission at 6 weeks and 3 months, and a low fecal calprotectin in a patient who is currently in remission appears to predict that remission will be maintained. In contrast, erythrocyte sedimentation rate and CRP measured at a particular point in time do not appear to predict future disease activity.

We do not yet understand the nature of the correlation between fecal biomarkers and endoscopic or histologic activity, but clinical trials to address this question are in progress, especially to determine whether interventions based on the results of fecal biomarkers will improve outcomes for the patient. It is hoped that fecal biomarkers will become the preferred method of assessment, instead of endoscopy and histology, since the main attraction of fecal biomarkers is the evaluation of mucosal inflammation without the need for an invasive procedure. Practice by some clinicians has already gone that way, and some gastroenterologists are using the change in fecal biomarker concentration as a prompt for decision-making, where the individual patient serves as his or her own control. For example, if a clinician is monitoring a patient who is well and has a low level of calprotectin but then finds a high level during a routine monitoring test, then this is likely to be an indicator that the patient is about to relapse, so therapy can be changed accordingly. That at least is the hope. Some of the many remaining questions are the test-retest interval, the magnitude of the change that has clinical relevance, which intervention—and whether fecal biomarker testing makes any difference at all.

G&H How do disease activity indices help clinicians to evaluate patients?

AW/ST Currently, we have several different symptom-based activity scores, as well as multiple composite scores that assess both endoscopy and clinical symptoms. One choice gastroenterologists face is whether to use separate indices for clinical symptoms, endoscopy, histology, and/or quality of life, or whether to use a composite index, such as the Mayo Clinic index, which combines clinical symptoms with endoscopy. The Mayo Clinic index is commonly used in clinical trials but has never been fully validated. While the apparent simplicity of a composite index is appealing since it reflects clinical practice, a disadvantage of any composite index is that it is difficult to validate individual components. Nevertheless, unvalidated derivations (such as the Mayo Clinic subscore, excluding endoscopy) have shown some association with patient-related outcomes in clinical trials. There are already validated indices for quality of life, endoscopy, and histopathology, but there is no validated index for clinical symptoms.

G&H Does the number of methods used to measure disease activity alter how a patient's disease is managed?

AW/ST Yes, very much so. By using a combination of indicators—whether clinical symptoms, endoscopy, histology, biomarkers, or quality of life—clinicians are more likely to get an accurate picture of the severity of the patient's disease. Clinicians can then adjust therapy accordingly to achieve the best outcome for the patient.

G&H Might decisions about clinical management differ depending on which methods are used to measure disease activity?

AW/ST How a patient's disease is evaluated could affect management decisions, but there are few data. The major problem with clinical disease activity indices is that there are so many of them: There are no less than 9 disease activity indices for UC. Much more work is needed to simplify, validate, and evaluate the sensitivity of change within these scores, as well as to determine the implications of a particular score on clinical decisions and/or outcomes.

We believe the first disease activity index to be tested in such a manner will rapidly become the standard; at present, however, trials commonly use not only different disease indices but also different endpoints. This makes it very difficult to compare and contrast trials. For example, the ACT 1 and ACT 2 trials used particular endpoints to evaluate whether infliximab was effective for the treat-

ment of UC; when these same endpoints were used to evaluate data from 2 large trials of mesalamine, remission rates increased from 22% (the efficacy reported when the mesalamine trials were initially published) to 50% (the efficacy reported when the data were re-evaluated using the ACT 1 and ACT 2 criteria). In this case, just using endpoints from a different trial almost doubled the apparent efficacy of a medication.

G&H Is there an accepted definition for remission in UC?

AW/ST No, definitions vary depending on whether remission is defined in the context of a clinical trial, a regulation, a guideline, or a clinical encounter. Even within the clinical trial context, a large number of endpoints have been used to define remission. Among variations on a theme, trials have defined remission as a Mayo Clinic score of 0, a modified Ulcerative Colitis Disease Activity Index (UCDAI) score less than or equal to 1, a UCDAI score less than or equal to 2, a Clinical Activity Index score less than or equal to 4, or a Mayo Clinic score less than or equal to 2 (with no subscore greater than 1). Given these differences, comparing studies is currently extremely difficult.

To help address this problem, a group of inflammatory bowel disease specialists from the United States, Canada, and Europe convened a couple of years ago and agreed that remission in UC should be defined as “complete cessation of rectal bleeding, urgency, and increased stool frequency, best confirmed by endoscopic and mucosal healing.” This statement seems reasonable and is readily understood by patients as absence of symptoms of UC confirmed by endoscopy. However, implementing such a definition requires converting it to an actual score on 1 of the disease activity indices, as well as it being adopted by clinical trial investigators.

G&H Is mucosal healing an essential aspect of remission?

AW/ST Yes, mucosal healing is essential when defining remission for patients with UC. Persistent mucosal inflammation is associated with a high risk of relapse, and mucosal healing (as assessed via the macroscopic appearance of the mucosa on endoscopy) appears to predict long-term remission. Mucosal healing may also decrease the risk of dysplasia or cancer, predict lower rates of hospitalization or surgery, and/or improve quality of life. On the other hand, whether mucosal healing is always “essential” in practice remains the subject of a discussion with individual patients and their expectations. That is where the art of medicine overtakes the science.

G&H What further research is needed in this area?

AW/ST We need international agreement as to which index or combinations of indices should be used to evaluate patients, and this consensus should include definitions of remission, mild disease, moderate disease, and severe disease. This will only happen with more data on the merits or demerits of particular indices and their relation to the outcomes that matter to patients. If the consensus is to use a composite index, the recently published UCEIS data should be taken into account, since use of a properly validated endoscopic index would bolster the validity of any composite index into which it may be incorporated. Alternatively, researchers could aim to validate a clinical symptom index, and clinicians could then use 4 different indices separately to assess clinical symptoms, endoscopy, histology, and quality of life, with a predefined composite outcome measure. A validated clinical index is the missing piece. Whatever index or indices are selected, there should

be international agreement on the basis for deciding on the index, inclusion criteria, and outcome parameters. Until such studies are conducted, the relative efficacy of different therapies for UC will remain difficult to compare.

Suggested Reading

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