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Remission in Trials of Ulcerative Colitis: What Does It Mean?

by Simon Travis and Lotte Dinesen

Measurement of disease activity in ulcerative colitis is critical in determining whether new therapies are effective, but there is no gold standard for measuring disease activity in ulcerative colitis. Not only is no single disease activity index widely accepted, but there is also no generally accepted definition of remission. Remission rates vary by as much as two-fold depending on the definition of remission. When two trials of 4.8 g mesalamine were evaluated according to the remission endpoint used for two trials of infliximab for active ulcerative colitis, apparent remission increased from 20.0% to 44.9%. Physicians and healthcare professionals should pay attention to the definition of remission being used as a measure of clinical efficacy in clinical trials. Interobserver variation in endoscopy scoring alone can influence the absolute remission rate by 10%–16%. Registration remission, which depends primarily on endoscopy and absence of rectal bleeding, is most subject to this influence. Clinical remission (absence of rectal bleeding and normal stool frequency) is used in clinical practice. Steroid-free remission is what matters to patients. The definition of remission needs to be validated if the results of clinical trials are to be compared.

The natural history of ulcerative colitis is characterized by relapses and remission. We all think we know what a relapse means. It's when a patient has symptoms of rectal bleeding diarrhea, tenesmus, urgency and abdominal pain before defecation. We all know what remission means, don't we? It's a normal bowel movement, stupid! Would that it were so simple—as Bill Clinton must have wished about the U.S. economy. The trouble is that it's a deal more complex, or otherwise clinical trials in ulcerative colitis wouldn't make such a meal of defining remission as an endpoint.

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The principal aims of medical treatment are to induce clinical remission when disease is active, then to maintain remission, and to reduce the risk of long-term complications (1). How good are we at achieving this? Long-term prognostic studies indicate that about 50% of patients with ulcerative colitis will be in remission at any given time, and 50% will relapse during the year; of these, 15% will have a severe relapse and 35%

a moderate relapse (2,3). From a patient's perspective, that's not very impressive. Furthermore, these favourable results are based on a treatment regimen of out-patient visits at least once yearly, a well defined strategy of maintenance mesalamine in all patients who can tolerate it and prompt treatment when relapse occurs. We have to do better and of course this means new treatments, subject to clinical trials.

The trouble is that there is no gold standard for measuring disease activity in ulcerative colitis. There are at least nine different scores used for evaluating activity (4). But, even before we start worrying about how we measure activity, we need to agree on a definition of remission. But because it is remission that matters to patients, the primary endpoint of clinical trials of ulcerative colitis should be steroid-free remission. This matters if clinical trials are to have direct relevance to patient management.

There are, in turn, at least three definitions of remission for ulcerative colitis. These may be termed clinical, registration and complete remission. Clinical remission is what is used in practice, meaning cessation of rectal bleeding and normal stool frequency. This is not the same as "registration" remission (the one currently, but not exclusively favored by the FDA), which means cessation of rectal bleeding and a sigmoidoscopy score of 0 or 1 (that equates to a normal appearance of the rectal mucosa, or erythema only). This, in turn is not the same as complete remission, which implies normal stool frequency, no rectal bleeding and a normal or quiescent appearances of the mucosa at sigmoidoscopy. The potential impact of these three definitions is considerable, but many trials simply use an arbitrary threshold to define the "remission" endpoint, either 0, 1 or 2 of one of the disease activity indices, or <150 in the complex Seo index (4). This makes it difficult to know what a trial means, because obscured in these low scores can be symptoms (such as bleeding or increased stool frequency) that clinicians and their patients would not recognize as remission. Furthermore, because most trials choose different endpoints, let alone different activity indices, comparing the results of different trials is exceptionally difficult.

Just consider the impact of different definitions of remission in one large patient cohort. The ASCEND studies included a total of 687 patients with mild to moderately active ulcerative colitis, treated with 2.4 g or 4.8 g mesalamine (5,6). In an analysis of the results using three different definitions of remission, the remission rate varied more than two-fold. When the Mayo disease activity index (DAI) was 0, it was 22% (in other words, "complete remission"; the DAI includes stool frequency, rectal bleeding, sigmoidoscopy, patient functional assessment and physician's global assessment); when the DAI was ≤1 the remission rate was 28% (meaning no bleeding and normal frequency, with at least a 1 point decrease in sigmoidoscopy score), but when "remission" meant a DAI ≤2, it was 50% (meaning no individual subscore >1) (7). This is an extraordinary degree of variation and no wonder that doctors and patients are confused by different activity indices of trials. Confusion is fostered by the different names for the different indices: the score used in this analysis was the Mayo score, also known as the Disease Activity Index, although the abstract itself erroneously refers to the Ulcerative Colitis Disease Activity Index (UCDAI) which is slightly different (4). At the end of the day, however, it is remission and not response that matters to the patient who has to get on a bus and travel with confidence. It is also steroid-free remission that matters.

Take the ACT trials of infliximab for ulcerative colitis refractory to standard therapy (8). Remission in the ACT trials was defined as a Mayo (DAI) score of two points or lower, with no individual subscore exceeding one point. This is the definition that allowed Asacol 4.8 g to score a remission rate of 50% in non-refractory ulcerative colitis (7). In the ACT 1 trial, the steroid-free remission rate after 7 months' treatment (30 weeks) with infliximab 5mg/kg every 8 weeks was 24.3% (17/70 patients) and 18.3% (11/60) in the ACT 2 trial. Of course this was twice that achieved by placebo (10.1% and 3.3%, both $p < 0.05$), but it's not as impressive as some would have us believe.

Now factor in interobserver-variation in sigmoidoscopy scoring, because this is a subjective assessment and inevitably subject to variation between different endoscopists. Indeed, Hugh Baron himself validated the original sigmoidoscopy scoring system in 1964 based on components where there was more than 60% "agreement" between four observers (9). This was before

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kappa statistics were applied to clinical measurement, but it illustrates the large potential for disagreement. This is a crucial issue for regulatory authorities, since the FDA currently favors a definition of remission for registration purposes based on sigmoidoscopy and rectal bleeding alone. When an independent observer evaluated the sigmoidoscopy videos of 335 patients in a recent therapeutic trial of ulcerative colitis, the observer disagreed with the investigators' sigmoidoscopy score in 12%–23% of cases (10). The impact on the remission rates of this variation in the sigmoidoscopy score was a median difference of 19.0% (range: 10.0% to 22.4%) for absolute clinical, complete and registration remission. If results were then analyzed according to the independent observer's score, remission rates were reduced in absolute terms by 10%–16% for registration, but by <3% for clinical or complete remission. It is not surprising that registration remission rates were most affected. The implications are substantial. It has the potential to make the difference between a therapeutically significant outcome and no response, and between licensed approval and no license.

Whilst addressing endpoints that matter to patients (and therefore their physicians), objective endpoints other than steroid-free remission should be considered when clinical trial measure remission. These include time off work or normal activities, hospital admission, colectomy and mortality. Of course the reason that these endpoints—and even the more readily attainable steroid-free remission—are not measured is that single drugs are unlikely to influence material outcomes that are subject to multiple external influences. Most randomized controlled trials involve single therapies sponsored by industry. That is one of the limitations of single-agent randomized controlled trials and is a reason for considering therapeutic strategies with several interventions, such as the chemotherapy regimens that have proved successful in haematological malignancies. Such trials are more complex with fewer vested interests from industry, but they bring clinical trials closer to the outcomes that matter to patients and their physicians. Everyday clinicians need to stand up and say that we don't like (or understand!) outcomes in clinical trials of ulcerative colitis and won't take it anymore.

So what is remission in ulcerative colitis? It depends on your perspective. It is either a low point in a scoring system for active disease that has to be used in clinical trials by way of necessity. Or it is a construct for achieving drug registration for regulatory authorities such as the FDA. Or it is something that is meaningful to patients, who can count the number of times they have to go to the bathroom each day, see whether there is visible blood in their stool, and understand what is meant by healing of the rectal mucosa. These are different needs: for a Phase II trial, response may be an adequate indicator of whether to pursue drug development. But for Phase III studies that lead to drug registration, steroid-free remission in terms that a patient can understand should be the primary endpoint. There is no reason that we should not have separate clinical, endoscopic, histological and quality of life indices of activity, rather than a composite index, as long as they are validated. We should start by validating remission on behalf of our patients. ■

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