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OBSERVATION

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Limitations in assessment of mucosal healing in inflammatory bowel disease

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Abstract

An emerging parameter to define the effectiveness of new therapeutic agents in clinical trials, and by extension, for use in day-to-day clinical practice has been labeled mucosal healing. It has been hypothesized that complete healing of the intestinal mucosa in inflammatory bowel diseases should result in reduced disease complications, reduced hospitalization and reduced surgical treatment. By implication, the natural history of inflammatory bowel disease might then be altered. Measurement of mucosal healing, however, is largely observational, requiring repeated invasive endoscopic examinations, sometimes with mucosal biopsies. Other indirect imaging methods may play a role in this assessment along with other surrogate markers, including intestinal permeability. These measurements may have significant limitations that prohibit precise correlation with symptom-based disease activity indices in clinical trials. This likely reflects the dynamic nature of this evolving and individualized inflammatory process that tends to be focused, but not limited, to the mucosa of the intestinal tract.

Key words: Intestinal mucosa; Digestive system endoscopy; Clinical trials

INTRODUCTION

Ulcerative colitis and Crohn's disease are inflammatory bowel disorders; both with no known cause. Curative treatment is still needed. As such, management has focused largely on ameliorating symptoms, and reducing hospitalization and the need for surgical treatment. In clinical trials, reductions of symptom-related numerical endpoints have been used [e.g. the Crohn's Disease Activity Index (CDAI)] as evidence of treatment effectiveness and their possible role in translation to clinical practice has been discussed previously[1-5]. Another treatment goal for these diseases is improving quality of life, based upon any means that this parameter might be clinically defined or measured. Now, an emerging measurement to define the effectiveness of new therapeutic agents in clinical trials, and by extension, for use in day-to-day clinical practice has been popularly labeled "mucosal healing".

In practical terms, the assessment of mucosal healing is based largely on observational evaluation, which requires the use of repeated endoscopic studies before and after a defined treatment period, sometimes in conjunction with histological examination of mucosal biopsies, or other more indirect imaging methods, other surrogate markers or miscellaneous methods, such as measurements of intestinal permeability. Logically, however, but not yet conclusively shown, complete healing of the intestinal mucosa should result over the long term in

reduced disease complications, hospitalization and surgical treatment. This proposed hypothesis further suggests that, if mucosal healing can be induced by treatment, then hopefully, the natural course and history of the disease in an individual patient might be modified, and by implication, improved. For example, in a Norwegian study[6], Crohn's disease or ulcerative colitis first diagnosed between 1990 and 1994 (before the use of biological agents) were examined endoscopically for up to 5 years. Mucosal healing after 1 year of treatment was reported in almost 50% of 495 treated patients that could be followed. Mucosal healing also appeared to predict reduced subsequent disease activity and a decreased need for active treatment in ulcerative colitis, but not Crohn's disease. Of note, the study also has demonstrated that other environmental factors may play an important role in mucosal healing (e.g. smoking, level of education).

ENDOSCOPIC INDICES

Earlier historical studies from Europe remain very important. These have shown considerable variability in endoscopic changes detected by experienced observers caring for patients with inflammatory bowel disease[7]. Moreover, the correlation between the patient's clinical status and endoscopic (and histopathological) changes in the colorectal mucosa was limited[8]. Later, using more modern measurements of disease activity (e.g. CDAI), there was a poor correlation between colonoscopic (or histological) findings and indices of disease activity, which implies that these were not reliable measures of disease severity or extent[9]. Similar results have been published by French investigators in a prospective evaluation of ileocolonic and colonic Crohn's disease[10]. In a later study[11], however, specific lesions were identified for evaluation that included: erythema, superficial and deep ulceration, stenoses and pseudopolypoid changes. Then, an index was calculated (Crohn's Disease Endoscopic Index of Severity; CDEIS), based on the percentage of involvement of different ileocolonic segments, for use in clinical trials of new therapeutic agents. A good correlation with lesion severity was reported with positive inter-observer agreement, but these investigators were very experienced and well trained for their study[11]. In routine day-to-day clinical practice, however, the reproducibility of this measurement seemed to be less helpful. As a result, other simplified endoscopic activity measures were proposed and applied in some clinical trials for Crohn's disease[12] and ulcerative colitis[13,14]. A detailed and excellent review of treatment indices, including endoscopic endpoints used in inflammatory bowel disease, specifically ulcerative colitis, has appeared elsewhere[15].

Definition of mucosal ulcers or erosions (or their apparent complete absence as a marker of mucosal healing) has been viewed by some clinicians with skepticism, given the highly fluid and dynamic nature of the inflammatory process in inflammatory bowel disease. Also, other factors may influence endoscopic evaluation, particularly for inflammatory bowel disease and its treatment (e.g. bowel preparation effects on the inflamed intestinal mucosa may differ from non-inflamed mucosa). In addition, the depth or extent of small-intestinal penetration at the time of visualization during ileocolonoscopy may not be well defined in some studies. For example, capsule endoscopy has demonstrated mucosal erosions or ulcerations distributed throughout the small intestine in Crohn's disease that are not appreciated well by other imaging modalities, including routine ileocolonoscopy[16]. Finally, a recent prospective evaluation in Crohn's disease confirmed that clinical response of the patient seemed to correlate poorly with capsule evaluation of the surface mucosa for assessment of healing[17].

Similarly, for ulcerative colitis, few well validated and well accepted endoscopic criteria for endoscopic mucosal healing have been evaluated for clinical trials. A large degree of overlap is evident within historical definitions of mild, moderate and severe endoscopic changes and, the degree of intra- and inter-observer error has been validated poorly in clinical trials, especially in multicenter studies with multiple observers involved in the evaluation of oral, intravenous or topical treatment regimens. In contrast, some studies have reported good inter-observer agreement for some, but not all endoscopic changes in ulcerative colitis, with experienced[18] as well as well-trained observers[19].

HISTOPATHOLOGICAL EVALUATION

In theory, microscopic definition of the mucosa provides precise evaluation of mucosal healing in response to treatment. However, this microscopic evaluation is not only dependent on endoscopic (or macroscopic) evaluation (for selection of the biopsy site), but is also prone to the impact of pathological inter- and intra-observer error. In Crohn's disease, this may be an especially significant problem owing to the focal or segmental nature of the inflammatory process. Even in ulcerative colitis, a disorder often characterized as a continuous inflammatory process, there may be a non-uniform pattern of mucosal healing. Little information is available on the temporal resolution of the inflammatory process, but it not likely to be uniform.

Moreover, the evaluation of the depth of inflammation may also be crucial to precise monitoring of treatment response. In Crohn's disease, this transmural dimension makes complete histopathological definition virtually impossible because endoscopic biopsies provide only mucosa for pathological evaluation. After treatment, this transmural pattern in Crohn's disease may be especially difficult to evaluate since medications may not affect the inflammatory process in a consistent or uniform fashion. Even with ulcerative colitis, a process thought to demonstrate a more continuous and mucosally based pattern of inflammation, variability in the histopathological severity within the colonic mucosa occurs. More precise studies are still needed that define the

mucosal response to different forms of injury and the healing response to different forms of treatment.

OTHER IMAGING METHODS

Invasive imaging studies, particularly repeated endoscopic studies, are normally not appealing to patients, and potentially, although rare, can still result in a procedure-related complication. Indeed, complications in patients with active inflammatory disease may exceed reported rates in otherwise healthy individuals undergoing screening procedures, and have been studied or reported poorly, particularly from treatment trials of new agents. Other less invasive approaches have often also been used in clinical practice, especially for repeated evaluations to assess the effects of therapy. These include imaging methods, such as computerized tomography (CT) and magnetic resonance imaging (MRI), usually with complete enterography. As with older barium imaging, however, there may be some inherent limitations. For example, these more modern imaging methods still have difficulty differentiating the inflammatory component of an intestinal stricture from its more established fibrotic component. CT may correlate with endoscopic evaluation for detection of ileal disease, but substantially increased radiation exposure results with repeated studies[20,21]. While both CT and MRI have limitations, multi-detector spiral CT enteroclysis may be more sensitive than MR enteroclysis for suspected bowel disease. In contrast, pelvic MRI has emerged as a standard for evaluation of perianal inflammatory disease or sepsis, particularly for fistula assessment and treatment[22]. Further correlation of these imaging modalities with other measures of intestinal healing are still needed.

OTHER NONINVASIVE METHODS

A number of surrogate markers have been promoted, including leukocytosis, thrombocytosis and C-reactive protein levels[23,24], but these are more clearly systemic rather than intestinal markers of the inflammatory process. Some of these markers also have been correlated with other indices. Other luminal markers, such as fecal lactoferrin or calprotectin[25], along with functional permeability measurements are available, and may provide a potentially important option for evaluation of healing, but need further evaluation.

TREATMENT ASSESSMENT

Placebo response and remission

In patients with inflammatory bowel disease, spontaneous clinical improvement or remission without treatment may occur. As a result, randomized placebo-controlled trials are done to determine if the investigative agent is superior to placebo treatment. Both patient and investigator are blinded to obviate bias. Placebo-based trials usually produce a positive effect even with placebo, in part, because of repetitive attention provided by caregivers to the trial subject. The placebo response is known to be powerful and, in a meta-analysis of placebo rates for inflammatory bowel disease clinical trials, rates up to 40% have been noted[26]. A superimposed issue in a clinical trial is the need to provide a proven form of therapy (while also testing the trial treatment). As a result, the placebo may, by necessity, be a standard therapy, not an inert treatment, while the treatment may include the standard therapy plus the trial treatment. For some medications, it may be difficult to hide the treatment because of known systemic effects (e.g. sulphasalazine or steroids). As noted elsewhere[26], placebo remission rates may also be influenced by trial length, number of study visits, use of strict remission definitions and enrollment favoring patients with more active disease.

Historical steroid studies

Early clinical trials with steroids have noted reduced clinical symptoms and improved appearances of the colonic mucosa[27,28]. Later trials with steroids have shifted the emphasis to the persistence of inflammatory changes, even though reduced symptoms were evident[29,30]. Unfortunately, the longer term role, if any, of steroids in mucosal healing and curbing the inflammatory process is understood poorly. In clinical practice, physicians limit the duration and dosage of systemic corticosteroids and taper these rapidly within weeks. This may not permit sufficient time for steroids to cause complete restitution of the mucosal surface. In a pooled treatment analysis of a first-pass metabolized steroid, budesonide, mucosal healing was reported to be limited in Crohn's disease after 1 year[31]. Budesonide, however, differs substantially in its chemical structure, metabolism and other properties from other steroids, therefore, generalization to other steroids may be premature. Some have hypothesized that steroids *per se* might be potentially deleterious to the mucosal healing process[32], but there is no evidence to support this view. It is possible that the observed healing effects of steroids only reflect the clinical tendency to minimize duration and dosage of systemic steroids because of fear of potential side effects.

Studies with other agents

Other agents used to treat inflammatory bowel disease, recently summarized in detail elsewhere for ulcerative colitis[33], also have been reported to cause endoscopic mucosal healing. These include 5-aminosalicylates, including a modernized formulation MMX mesalamine[34,35], immunosuppressant agents in Crohn's disease, such as azathioprine and methotrexate[36-40], antibiotics[41,42], and even prolonged courses of anti-mycobacterial treatment in Crohn's disease[43]. Similarly, biological agents are now being evaluated and mucosal healing has been reported as an important endpoint of treatment in the clinical trials[44-46]. Most of these studies, along with initial reports of other biological agents, have been conducted over only limited time frames, relative to the

natural duration of the disease, so positive and negative effects over the long term are not evident. In a recent report from a cohort in a treatment trial that has compared infliximab and azathioprine to conventional therapy with steroids, complete mucosal healing, defined as a simple endoscopic score[12] of 0 after 2 years of treatment predicted a sustained remission 3 and 4 years after therapy in > 70% of patients, compared to almost 30% of those with endoscopic lesions[47]. Of note, the authors also have concluded that achieving mucosal healing (defined by endoscopy) was the sole determining predicting factor and not the treatment *per se*.

FUTURE DIRECTIONS

A number of issues need to be addressed carefully in the near future. Therapeutic trials of differing pharmacological and biological agents in inflammatory bowel disease have shown that mucosal healing may occur with most of the traditional drugs, as well as the emerging biological agents, to a greater or lesser degree, but correlation with the patient's symptoms or other measures of disease activity appear to be limited. The current technology to assess mucosal healing in clinical trials and clinical practice remains limited, tends to be observational, and is not ideal because it does not evaluate transmural inflammation precisely, only the luminal surface mucosa. Repeated invasive endoscopic evaluations may not be optimal, particularly since these are largely one-dimensional. Possibly, this will be improved with the future evolution of confocal endoscopy. The inflammatory process is not a static target and the measured impact of one or the other agent may reflect, in part, this fluidity of the inflammatory process *per se*. As a result, assessing the longer-term effects of old and emerging agents is needed urgently, but may also prove to be particularly challenging. Genome-wide expression differences have been defined using endoscopic pinch biopsies in both ulcerative colitis and Crohn's disease[48]. These ultimately may provide a means for selecting individuals with either ulcerative colitis or Crohn's disease that might be managed optimally with a specific therapy, because multiple genes appear to be involved[49]. New studies have appeared employing microarray technology in animal and human colitis, which have increased our understanding of the basic inflammatory process, along with possible mediators that might be regulated[50-53]. Indeed, very recent genome-wide association studies in ulcerative colitis have identified new susceptibility loci that suggest that changes in the integrity of the mucosal barrier are important in pathogenesis[54]. By recognizing the limitations of current methodology used in clinical trials to assess mucosal healing, the modern day clinician will still have to rely on his or her clinical evaluation and best judgment whenever a new treatment paradigm is contemplated, or a change or cessation in therapy is indicated. Fortunately, however, emerging gene-based technology is likely to lead to better end points for more precise assessment of available treatments.

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