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Review article

Mucosal healing in inflammatory bowel disease: Treatment efficacy and predictive factors

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ABSTRACT

In recent years mucosal healing has emerged as an important therapeutic goal for patients with inflammatory bowel disease. Growing evidence suggests that achieving mucosal healing can improve patient outcomes and, potentially, alter the course of the disease. Drugs currently used in the management of inflammatory bowel disease are potentially able of inducing and maintaining mucosal healing, but the effect size is difficult to assess because of different definitions of mucosal healing, differences in study designs, and timing of endoscopic evaluation. Mucosal healing has been studied extensively in the biologic era. Data available from different sources, such as controlled trials and observational studies, show that anti-TNFα therapies can induce rapid and sustained mucosal healing in a variable percentage of patients with Crohn's disease and ulcerative colits. No controlled study has been designed to identify possible predictors of mucosal healing. Some clinical characteristics such as extensive disease, young age at diagnosis, and smoking status may be predictive of a more aggressive clinical course and, presumably, of a reduced clinical and endoscopic response to therapy. Changes and normalization of C-reactive protein and faecal calprotectin may be useful tools to predict outcomes, guide the timing for endoscopic evaluation and, possibly, reduce the need of endoscopic evaluation in assessing mucosal healing.

1. Introduction

Since the 1960s, clinical studies suggested that in ulcerative colitis (UC) patients the long-term outcome after a steroid course was more favourable in patients who achieved both clinical and endoscopic remission compared to those who achieved clinical remission only [1]. Up to the late 1990s, other observational studies reported the lack of a similar correlation in patients with Crohn's disease (CD). In particular, these studies described the absence of a clear impact of healing of the mucosal lesions on relapse rates in CD patients with steroid-induced clinical remission [2]. These observations led clinicians to limit their CD treatment focus to symptomatic remission, therefore abandoning the idea that mucosal healing (MH) could affect the natural course of the disease.

The attitude of clinicians towards MH changed drastically when anti-TNFα drugs entered the clinical scenario of inflammatory bowel disease (IBD). For the first time, in fact, it was thought possible to achieve rapid healing of mucosal lesions also in CD [3]. Since then, the interest on MH grew so much that nowadays there is a trend towards considering MH a clinically relevant end point for both UC and CD treatment strategies. As a consequence of this growing interest around MH, some studies have retrospectively investigated the importance and impact of MH in the pre-biologic era. In particular, a Norwegian population-based cohort study showed that the presence of MH 1 year after the diagnosis of IBD predicted a significant reduction in surgery rates in the subsequent years [4].

In recent years, several clinical trials have examined the ability of various agents to heal the mucosa in CD and UC. However, interpreting these studies can be difficult given the differences in study design, the lack of a standardized definition of MH and different timing of endoscopic evaluation.

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2. Current treatments for IBD and MH

2.1. Aminosalicylates and MH

There are no data on aminosalicylates-induced MH in CD. Presumably, these drugs are not able to induce MH and, although well tolerated, their clinical efficacy in the long-term treatment of CD is lacking [5]. Conversely, several data prove the capacity of both oral and rectal aminosalicylates of inducing MH in mild to moderately active UC. Regarding topical 5-aminosalicylic acid (5-ASA), a meta-analysis of 10 studies showed that 36% of patients receiving topical 5-ASA for 2–6 weeks achieved endoscopic remission compared to 17% of patients receiving placebo [6]. As far as oral 5-ASA is concerned, the percentage of endoscopic remission reported in several studies ranges from 25% to 70%, although different 5-ASA doses and formulations, different definitions of MH, and different time points of endoscopic evaluation have been used [7–9]. In a recent meta-analysis involving 3977 patients treated with oral 5-ASA and 2513 patients treated with rectal 5-ASA, the overall rate of MH was 36.9% in patients receiving oral 5-ASA and 50.3% in patients receiving rectal 5-ASA [10].

From a recent revision of the ASCEND I and II trials comparing 2 different 5-ASA doses for inducing remission in 391 patients with mild to moderately active UC, it emerged that, after 6 weeks of treatment, MH (defined as a Mayo sub-score of 0 or 1) was achieved in 80% of patients receiving 5-ASA 4.8 g/day and in 68% of patients receiving 5-ASA 2.4 g/day ($p = 0.012$). When MH was defined more strictly as a Mayo sub-score equal to 0, these rates dropped to 32% and 24%, respectively, with no statistical difference between the 2 doses [11].

Another attempt to quantify the efficacy of aminosalicylates preparations in inducing MH was made by combining the results of 2 randomized, double-blind, placebo-controlled trials that tested multi matrix system (MMX) mesalazine on 517 patients with mild to moderately active UC [12]. Complete or partial MH (defined as ulcerative colitis-disease activity index, UCDAI ≤ 1) was achieved in 76% of patients receiving mesalazine MMX 4.8 g/day, 70% of patients receiving mesalazine MMX 2.4 g/day, and 44% of patients receiving placebo ($p < 0.05$). Considering a more strict definition of endoscopic remission (UCDAI = 0) the corresponding figures were 32%, 32%, and 16%, respectively [12]. Results of these pooled analyses are summarized in Fig. 1.

Recently, in a prospective observational study [13], 81 patients with mild to moderately active UC received 5-ASA 4 g/day orally and 2 g/day per rectum for 6 weeks. Sixty-one patients (75%) achieved clinical remission whereas endoscopic activity was still present in only 5 patients (8%). The cumulative rate of relapse at 1 year was 23% in patients with clinical and endoscopic remission and 80% in patients without endoscopic remission ($p < 0.0001$).

2.2. Corticosteroids and MH

It has been known for a long time that steroids, despite their excellent capacity to induce clinical remission, are not powerful in inducing MH in CD. An historical trial evaluated the endoscopic status of 131 patients with ileocolonic CD and steroid-induced clinical remission. Endoscopic examination revealed that, after steroid treatment, only 29% of patients in clinical remission were also in endoscopic remission, while the remaining 71% had persistence of endoscopic activity [14]. Across the pre-biologic era, this pivotal study reinforced the impression that MH could not be reached in CD and therefore should not be pursued as an end point. Conversely, in UC, an equally important historical trial published by Truelove et al. in 1955 showed that steroids were capable of inducing normalization or improvement of the endoscopic findings. Endoscopic remission was reached in 30% of patients receiving steroids vs 10% of patients receiving placebo ($p = 0.02$); endoscopic improvement was observed in 22% vs 21% of patients, respectively, and no change or worsening of endoscopic findings was found in 48% vs 68% of patients, respectively [15].

Recently, a prospective trial conducted by Ardizzone et al. on 157 UC patients at their first steroid course showed that approximately 35% of patients achieved both clinical and endoscopic remission, 25% of patients achieved clinical but not endoscopic remission, while another 35% of patients failed to respond to steroids. In this study the endoscopic activity was evaluated by means of the Baron score: endoscopic remission was defined as a Baron score equal to 0. The same patients were followed up for up to 60 months and the Kaplan–Meier analysis revealed that patients with both clinical and endoscopic remission had a better outcome compared to patients with only clinical remission in terms of need of immunomodulators, hospitalization, and surgery [16]. In conclusion, these data from historical and recent studies suggest a different effect of corticosteroids on MH induction and long-term outcome in UC and CD.

2.3. Immunomodulators and MH

Azathioprine (AZA) is usually considered effective in inducing MH in CD, even though it is well known that this drug takes a long time to achieve its potential benefits. However, evidence for AZA-induced MH in CD is very limited, deriving from 2 small retrospective studies [17,18]. The first study included 15 patients with post-operative recurrence of ileitis who had been treated with AZA for more than 6 months. MH was observed in approximately 40% of patients after a median time of 18 months (17.9 ± 5.6 months) [17]. In the second study 20 CD patients were treated with AZA for at least 9 months and, after a median time of treatment of approximately 2 years, 54% of patients showed healing of the mucosal lesions located in the ileum and 70% of patients showed healing of the colonic lesions [18].

In a prospective study from the GETAID (Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives), designed to assess the long-term outcome after AZA withdrawal in patients with CD in remission, 83 patients in clinical remission under AZA for at least 42 months were randomized to continue AZA or to receive placebo. The primary end point was the relapse rate over 18 months. At baseline, a subgroup of 45 patients underwent endoscopic evaluation. Complete MH, strictly defined as a Crohn's disease endoscopic index of severity (CDEIS) = 0, was observed in only 16 of 45 patients (36%), whereas in patients with endoscopic activity, despite stable clinical remission, ulcerations were still present in 21 of 45 patients (47%) [19].

A prospective open study published by Mantzaris et al. in 2009 was conducted on 77 patients with steroid-dependent CD who had achieved clinical remission with steroids. These patients were randomized to receive either budesonide or AZA as maintenance treatment for 1 year and endoscopic and histological activity were assessed at baseline and at study end. On per protocol analysis, 83% of AZA-treated patients achieved complete or near-complete MH compared to 24% of budesonide-treated patients ($p = 0.0001$). On intention-to-treat analysis, and considering only complete MH, the percentage of patients with AZA-induced MH was 58% [20].

In the SONIC study [21], which compared AZA, infliximab (IFX), and the combination therapy in moderate to severe CD, MH was a secondary end point and it was assessed in a subset of patients who underwent endoscopy at baseline and at week 26. Only 16% of patients receiving AZA monotherapy achieved complete MH.

Results of studies with AZA in CD evaluating MH are summarized in Fig. 2.

Regarding UC, a randomized controlled trial (RCT) published in 2006 by Ardizzone et al. compared AZA with 5-ASA for the