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SPECIAL ARTICLE

Results from the 2nd Scientific Workshop of the ECCO (I): Impact of mucosal healing on the course of inflammatory bowel disease

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Abstract

Over the past years, mucosal healing has emerged as a major therapeutic goal in clinical trials in inflammatory bowel diseases. Accumulating evidence indicates that mucosal healing may change the natural course of the disease by decreasing the need for surgery and reducing hospitalization rates in both ulcerative colitis and Crohn's disease. Mucosal healing may also prevent the development of long-term disease complications, such as bowel damage in Crohn's disease and colorectal cancer in ulcerative colitis. Histologic healing may be the ultimate therapeutic goal in

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ulcerative colitis, whereas its impact on the course of Crohn's disease is unknown. Complete mucosal healing may be required before considering drug withdrawal. Targeting early Crohn's disease is more effective than approaches aimed at healing mucosa in longstanding disease. Several questions remain to be answered: should mucosal healing be systematically used in clinical practice? Should we optimize therapies to achieve mucosal healing? What is the degree of intestinal healing that is required to change the disease course? Large prospective studies addressing these issues are needed.

Contents

1. Introduction

Over the past decades, several studies looked at mucosal healing (MH) in inflammatory bowel diseases. The scientific committee of ECCO has launched in 2010 a scientific workshop that focused on this significant clinical research question. The overall objective was to better understand and explore the importance of mucosal healing in inflammatory bowel disease. The outcome of this workshop is presented into four parts: Mechanisms of Intestinal Healing (Basic science), Measures and Markers of Prediction to achieve, detect, and monitor Intestinal Healing, Impact of Intestinal Healing on the Course of IBD (Natural history), and Therapeutic Strategies to enhance Intestinal Healing (Therapy). This manuscript summarizes current knowledge regarding the impact of mucosal healing on the course and management of inflammatory bowel diseases and highlights several key issues that need to be addressed in future studies.

2. How important is MH in the course of the disease? (Table 1)

2.1. Is MH associated with better clinical response rates?

With regard to Crohn's disease, D'Haens et al. reported in a substudy of the ACCENT 1 trial that patients who were achieving MH with infliximab had a longer relapse-free survival than those patients whose MH was not reached.[1] In a retrospective single center cohort study reporting the long-term outcome of infliximab in 214 patients with Crohn's disease,[2] patients achieving MH experienced a sustained clinical benefit more frequently compared to patients who

Table 1 How important is mucosal healing in the course of the disease?

Key messages
- Mucosal healing is associated with lower relapse rates
- Mucosal healing is associated with lower hospitalization rates
- Mucosal healing is associated with less bowel damage (fistulas) in Crohn's disease
- Mucosal healing is associated with reduced need for surgery
- Mucosal lesions predict postoperative clinical recurrence in Crohn's disease
- Mucosal healing is associated with lower risk of colorectal cancer in ulcerative colitis

Questions to be addressed in the future
- What is the impact of mucosal healing on bowel damage (stricture, abscess and fistula) in Crohn's disease in prospective studies? What is the best timing for endoscopic evaluation in the postoperative setting in Crohn's disease?
- What is the impact of mucosal healing on the risk of colorectal cancer in Crohn's disease?

Table 2 Should we adapt our therapy based on mucosal healing?

Key messages
- Mucosal healing is associated with lower relapse rates following drug withdrawal in infliximab-treated patients with Crohn's disease
- Histologic healing is associated with better outcomes in ulcerative colitis
- Greater mucosal healing rates are achieved in early Crohn's disease

Questions to be addressed in the future
- Should therapies be optimized to achieve mucosal healing?
- Is sustained mucosal healing required to change the course of the disease?
- What is the degree of mucosal healing that is required to modify disease course?
- What is the impact of histologic healing on the course of Crohn's disease?
- What is the impact of disease duration of mucosal healing rates in ulcerative colitis?

did not achieve MH after a median follow-up of 69 months (64.8% vs. 39.5%, respectively, p=0.0004). Also, the long-term follow-up of the step-up/top-down trial[3,4] showed that patients achieving MH at 2 years remained in steroid-free clinical remission during the following 2 years more frequently compared to patients with persistent endoscopic activity at 2 years by combining the two treatment arms (71% vs. 27%, respectively, p=0.003).

Already in 1966, Wright et al. reported that patients with ulcerative colitis who did not achieve MH under oral and rectal steroids relapsed more frequently during a follow-up period of 1 year compared to patients who did achieve MH (40% vs. 18%, respectively).[5] In the ACT1 and ACT2 trials,[6,7] the proportion of infliximab-treated patients with ulcerative colitis in clinical remission at week 30 was fourfold greater for patients with MH at week 8 (48.3% vs. 9.5%, respectively). In a Japanese study including 56 patients who achieved clinical remission after leukocytapheresis for ulcerative colitis and followed-up during a median of 22 months, significantly higher sustained clinical remission rates were reported among patients who had also achieved MH.[8] In an Italian cohort enrolling patients with ulcerative colitis, those not achieving endoscopic remission at 3 months had a higher cumulative probability of clinical relapse (73.9 vs. 27.5%, respectively, p<0.001).[9]

Data on MH in pediatric Crohn's disease and ulcerative colitis are scarce.[10] A retrospective pediatric study has compared the effect of step-up and top-down strategies in 32 children with newly diagnosed Crohn's disease. The CDEIS score was lower in patients receiving infliximab therapy (6.5) than in those receiving non-biologic therapy (12.4) and the rate of clinical relapse at 1 year was significantly lower in the top-down group receiving infliximab therapy.[11]

A pediatric retrospective study looked at 37 children who received exclusive enteral nutrition, comparing outcomes in these children to those of 10 children treated with steroids. Children managed with exclusive enteral nutrition achieved greater MH (64.8% vs. 40%) and had a longer duration of remission in the 12-month follow-up period.[12] Data on MH in pediatric ulcerative colitis are eagerly awaited.

MH is associated with higher clinical response and lower rates of relapses in both Crohn's disease and ulcerative colitis.

2.2. Is MH associated with fewer hospitalizations?

In the endoscopic substudy of the ACCENT I trial, patients achieving MH at both weeks 10 and 54 needed less Crohn's disease-related hospitalizations (0.0%) compared to those with MH at only one of both visits (18.8%) or with no healing at either visit (28.0%).[13] In a retrospective single center cohort study evaluating the long-term outcome of infliximab in 214 patients with Crohn's disease,[2] patients who achieved MH needed hospitalization less frequently compared to patients who did not (42.2% vs. 59.3%, respectively, p=0.0018).

In ulcerative colitis, Ardizzone et al. showed that no MH after first course of corticosteroid therapy was associated with a more aggressive disease course. Indeed, after multivariate analysis, lack of MH was the only factor associated with negative outcomes at 5 years, including hospitalization (HR, 3.634; 95% CI, 1.556–8.485; P=0.0029).[14]

MH is associated with lower hospitalization rates in both ulcerative colitis and Crohn's disease.

2.3. Does MH prevent complicated disease behavior in Crohn's disease?

There is no or scarce data on the impact of mucosal healing on disease behavior in Crohn's disease. In a retrospective study evaluating 102 patients with Crohn's disease, the presence of deep ulcerations at index ileocolonoscopy was associated with a higher risk of developing penetrating disease after a median follow-up of 52 months (Log Rank p=0.003).[15]

Significant mucosal lesions at diagnosis might indicate complicated disease behavior. However, large prospective studies are needed to further investigate whether MH may prevent complications in Crohn's disease.

2.4. Is MH associated with a reduced need for surgery?

In Crohn's disease, the presence of deep ulcerations at index ileocolonoscopy was associated with a higher risk of surgical resections after a median follow-up of 52 months (relative risk (95% CI): 5.43 (2.64–11.18), p<0.0001).[15] In a retrospective single center cohort study evaluating the long-term outcome of infliximab in 214 patients with Crohn's disease,[2] patients who had achieved MH needed major abdominal surgery less frequently than those who

did not achieve MH (14.1% vs. 38.4%, respectively, p<0.0001). In a Norwegian population-based cohort study,[16] 11% of Crohn's disease patients with MH at 1 year needed a surgical resection by 5 years compared to 20% of patients without MH (p=0.10).

In 1980, Buckel et al.[17] found that while there was a tendency for anorexia, abdominal tenderness on palpation, fever, tachycardia, leukocytosis, and hypoproteinemia to occur more commonly as the depth of ulceration increased in acute colitis, no single feature or combination of these features correlated well with ulcer depth. More recently, in a French study,[18] 23% of the patients without deep ulceration were submitted to surgery in comparison to 93% of those with deep ulceration. Subsequently, the same group confirmed that the presence of severe endoscopic lesions was independently associated with increased colectomy rates in acute severe ulcerative colitis.[19] In another French study enrolling 118 patients with steroid-refractory ulcerative colitis, the presence of severe endoscopic lesions was an independent predictive factor of colectomy (adjusted hazard ratio=2.38, 95% confidence interval 1.80–3.14).[20] A Japanese study including patients with intravenous steroid refractory ulcerative colitis found lower colectomy rates at 1 year among subjects with mucosal improvement at day 14 (p<0.01).[21]

Over the past years, some studies evaluated the impact of mucosal lesions on the need for colectomy in ulcerative colitis outside the setting of acute severe colitis. In a retrospective single center study, a longer colectomy-free survival was observed among ulcerative colitis patients who achieved MH at week 4 or 10.[22] In a substudy of the ACT1 and ACT2 trials, a lower colectomy rate was reported within the first 54 weeks of follow-up in patients with ulcerative colitis randomized to infliximab compared to placebo (10% vs. 17%, respectively, p=0.02).[23] In a Norwegian population-based cohort study,[16] 2% of ulcerative colitis patients with MH at 1 year needed a surgical resection by 5 years compared to 7% of patients without MH (p=0.02). Ardizzone et al. showed that the lack of MH after first course of corticosteroid therapy was associated with higher need for colectomy in newly diagnosed ulcerative colitis (HR, 8.397; 95% CI, 1.278–55.186; p=0.0268).[14]

MH is associated with a reduced need for surgery in both Crohn's disease and ulcerative colitis.

2.5. Can MH predict clinical postoperative recurrence in Crohn's disease?

In 1990, Rutgeerts et al. demonstrated in a prospective cohort that endoscopic lesions within the first year after an ileocolonic resection for Crohn's disease predicted postoperative clinical recurrence.[24] Throughout follow-up, symptomatic recurrence occurred less frequently in patients who had no severe endoscopic lesions at 1 year (Rutgeerts' score 0 or 1) compared to patients with a more severe endoscopic recurrence (Rutgeerts' score ≥i2).

In severe recurrent ileitis treated with azathioprine, the therapy resulted in induction and maintenance of clinical remission in all 15 patients. However, complete macroscopic healing of the neoterminal ileum was observed in 6 patients, near-complete healing with only superficial erosions remaining in 5 patients, partial healing in 3 of 15 patients, and unchanged inflammatory lesions in one patient, suggesting that partial healing may be sufficient to prevent clinical recurrence.[25]

Yamamoto et al. investigated the impact of enteral nutrition on clinical and endoscopic recurrence after surgical resection for pediatric Crohn's disease[26]. Forty consecutive patients who underwent resection for ileal or ileocolonic Crohn's disease were randomized to receive partial enteral nutrition or a regular diet. Twelve months after surgery, endoscopic recurrence was observed in six patients (30%) in the enteral nutrition group compared to 14 (70%) in the non-enteral nutrition group (P=0.027). One patient (5%) in the enteral nutrition group and 7 (35%) in the non-enteral nutrition group developed clinical recurrence during the 1-year follow-up (P=0.048) [26]. Thus, long-term enteral nutrition supplementation may significantly reduce clinical and endoscopic recurrence after resection for Crohn's disease.

Endoscopic postoperative recurrence predicts a worse outcome in Crohn's disease. However, the optimal timing for endoscopic evaluation remains unclear.

2.6. Is MH associated with less colorectal cancer?

In an epidemiological, case–control study including 68 patients with longstanding extensive ulcerative colitis who were matched to 136 controls, histological inflammation score was the only independent risk factor for the development of colorectal neoplasia (Odds ratio (95% CI): 4.69 (2.10–10.48), p<0.001).[27] In a subsequent study, Rutter et al. showed that macroscopically normal endoscopic findings returned the 5-year cancer risk to that of the general population (Odds ratio (95% CI): 0.38 (0.19–0.73), p=0.003).[28] Rubin et al. also demonstrated a higher risk of cancer and dysplasia in ulcerative colitis patients with a higher inflammatory activity score (Odds ratio (95% CI): 2.73 (1.44–5.18), p=0.002).[29] Gupta et al. confirmed that histological inflammation over time was associated with the progression towards advanced neoplasia in ulcerative colitis (Hazard ratio 3.0; 95% CI : 1.4–6.3).[30]

MH is associated with a lower risk of colorectal cancer in ulcerative colitis. Such data is lacking in Crohn's disease.

3. Should we adapt our therapy based on MH? (Table 2)

3.1. Can MH be used to optimize disease management outcomes?

The GETAID[31] demonstrated that in Crohn's disease patients who had achieved clinical remission, adjustment of steroid

treatment duration on the basis of endoscopic results presented no benefit, and that the endoscopic aspect had no prognostic value.

In the ACCENT 1 trial, Crohn's disease patients (n=9) who had MH at both weeks 10 and 54 did not require any hospitalization. Interestingly, patients with MH at only one visit required fewer hospitalizations (18.8%) compared to those without MH at both visits (28%), highlighting sustained MH as a new therapeutic goal in Crohn's disease.[13]

Although MH, at least under anti-TNF-a therapy is associated with fewer hospitalisations, the question whether therapies should be optimized based on endoscopic evaluation to improve disease outcomes remains open and will require further investigation.

3.2. Is MH associated with less relapse after drug withdrawal?

In a placebo-controlled study by the GETAID including 83 patients in clinical remission under azathioprine, presence of ulcerations at ileocolonoscopy before discontinuation of azathioprine was not predictive for clinical relapse.[32] Recently, in another GETAID trial, Louis et al. assessed the risk of clinical relapse after discontinuation of infliximab in 109 patients with Crohn's disease who were in clinical remission under a combined maintenance therapy with infliximab and an immunomodulator (azathioprine or methotrexate).[33] In multivariate analysis, in contrast to the former study investigating relapse after azathioprine withdrawal, complete MH was among the factors strongly associated with a decreased risk of clinical relapse after infliximab withdrawal (Hazard ratio (95% CI): 2.6 (1.3–5.3), p=0.005). In this study, immunosuppression with azathioprine or methotrexate was continued.

In Crohn's disease, MH is associated with a lower relapse rate after drug withdrawal, even though this may depend on the type of drug. The degree of mucosal healing which needs to be achieved remains to be determined. With regard to ulcerative colitis, such data is lacking.

3.3. What is the impact of the degree of intestinal healing on disease course?

Importantly, Schnitzler et al.[2] have shown that MH predicts long-term outcome with maintenance therapy with infliximab in Crohn's disease. The need for surgery was significantly different between the groups with and without MH (14% and 38.4%, respectively, p<0.0001). Interestingly, there was no difference between the groups with complete and partial MH (14% vs. 14.1%, respectively).

There is good evidence that infliximab can lead to histological improvement in mucosal biopsies in Crohn's disease. Di Sabatino et al.[34] examined the effect of infliximab in Crohn's disease patients 10 weeks after treatment initiation. Six out of 10 patients had clinical response and this correlated well with macrophage matrix metalloproteinase (MMP) expression levels in the mucosal biopsies along with histological score improvement (2.66+/−0.51 at baseline to 0.16+/−0.40 at week 10). Non responders (n=4) conversely revealed no histological improvement. Similarly, D'Haens et al. have shown a good correlation between histological and endoscopic healing after infliximab in a European Multicentre trial.[35] The CDEIS correlated with histological score 4 weeks after infliximab therapy (r=0.56, p=0.002). However, the impact of histological healing among infliximab-treated patients with Crohn's disease is unknown.

Patients with ulcerative colitis who were in clinical remission but with histological evidence of mucosal inflammation (acute inflammatory cell infiltrate, crypt abscess or mucin depletion) had a 2–3 fold greater risk for clinical relapse during a 1-year follow-up period compared to those with histological healing.[36] In another study among ulcerative colitis patients,[37] basal plasmacytosis on rectal biopsy was as an independent predictor of clinical relapse during a 1-year follow-up period (hazard ratio (95% CI): 4.5 (1.7–11.9), p=0.003).

Whether complete or partial MH is required to modify the disease course will require further investigation. Histologic healing is associated with a better outcome in ulcerative colitis, whereas its impact on disease course remains to be investigated in Crohn's disease.

3.4. What is the impact of disease duration and disease extent on MH rates?

In the EXTEND trial, among 123 Crohn's disease patients with mucosal ulceration at baseline, the rate of MH at week 12 was higher in subjects with disease duration less than 2 years than in those with disease duration greater than 5 years (44 vs. 21%, respectively) in the adalimumab arm.[38]

D'Haens et al. found similar rates of complete MH in the ileum and in the colon of Crohn's disease patients under azathioprine for at least 9 months.[39] In the IBSEN population-based cohort, disease extension and location did not influence MH rates in Crohn's disease patients.[16] By contrast, patients with extensive disease were more prone to reach MH as compared to those with left-sided colitis and proctitis.[16] The relationship between disease extension and mucosal healing in this study may be partly explained by a more aggressive treatment in patients with extensive colitis. Rates of MH according to disease extent could not be investigated in randomized, controlled trials as mucosal lesions are usually assessed by proctosigmoidoscopy in ulcerative colitis.

Greater MH rates may be achieved in early Crohn's disease, even though only data from subgroup analyses are available. The impact of disease duration on MH has never been investigated in ulcerative colitis.

4. Conclusion

MH is associated with better outcomes in inflammatory bowel diseases (clinical response/remission, hospitalizations, surgery). Some evidence indicates that MH may also reduce the development of bowel damage such as fistulas in Crohn's disease and the incidence of colorectal cancer in ulcerative colitis. Several issues remain unresolved. Should MH be systematically assessed to improve disease outcomes? In this regard, large prospective studies assessing the impact of MH and histologic healing on the natural course of inflammatory bowel diseases in the era of biologics are eagerly awaited. Another question remains open: should we optimize therapies based on endoscopic findings to change the disease course? Lastly, the timing of endoscopic evaluation and the concept of sustained MH will also require further investigation.

Conflict of interest

LPB, consulting and lecture fees from Merck and Abbott; MF, consulting and lecture fees from Merck, Centocor and Abbott; FM, lecture fees from Merck, Abbott, and Falk; SC, consulting and lecture fees from MSD, Abbott; HS, consulting and lecture fees from, Abbott, MSD and AstraZeneca; SA, none; GVW, consulting and lecture fees MSD, Danone, J&J; JBC, none; MA, consulting and lecture fees from Abbott, lecture fees for Merck; SD, consultant and lecture fees from Schering-Plough, Abbott Laboratories, UCB, Ferring, Cellerix, Millenium Takeda, Nycomed, Actelion, Astra Zeneca, Novo Nordisk, and Cosmo Pharmaceuticals; AS, consulting and lecture fees from Merck, Abbott, Falk, Ferring, Viofer, Shire; the other authors did not state any conflict of interest.

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- AS and LPB organized the group meeting, on behalf of the ECCO scientific committee, drafted and edited the manuscript.
- All the authors wrote specific parts of the manuscript.
- All authors read and approved the final manuscript.

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