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Abstract: Nowadays, mucosal healing is regarded as a major end point in clinical trials and is increasingly used in clinical practice for the management of patients with inflammatory bowel disease. The definition of mucosal healing varies across studies and validated endoscopic scoring indices are still lacking. The advent of anti-tumor necrosis factor agents has changed the way of treating inflammatory bowel disease and high rates of induction and maintenance of mucosal healing can be achieved with this drug class. Mucosal healing is desirable as it may change the natural course of the disease by decreasing surgery and hospitalization rates in both ulcerative colitis and Crohn's disease.

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Mucosal healing with anti-TNF antibodies

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Key words: Mucosal healing, Crohn's disease, ulcerative colitis, anti-TNF

ABSTRACT

Nowadays, mucosal healing is regarded as a major endpoint in clinical trials and is increasingly used in the management of patients with inflammatory bowel disease (IBD) in clinical practice. Definition of mucosal healing varied across studies and validated endoscopic scoring indexes are still lacking. The advent of anti-Tumor Necrosis Factor agents has changed the way of treating IBD and high rates of induction and maintenance of mucosal healing can be achieved with this drug class. Mucosal healing is desirable as it may change the natural course of the disease by decreasing surgery and hospitalization rates in both ulcerative colitis and Crohn's disease.

Initial lack of correlation between mucosal healing (MH) and clinical remission in inflammatory bowel diseases (IBD) patients led the clinician to abandon this concept [1]. The advent of anti-Tumor Necrosis Factor (TNF) agents has changed the way of treating IBD. Anti-TNF therapy allows rapid symptoms improvement but also mucosal healing (MH) [2]. Accumulating evidence indicates that MH may change the course of both Crohn's disease (CD) and ulcerative colitis (UC) [3-5]. Accordingly, MH is now regarded as an important treatment end point in clinical trials and is increasingly used in clinical management of IBD [6].

After discussing available definitions of MH, we will review the efficacy of anti-TNF antibodies to induce and maintain MH before highlighting the positive impact of MH on long-term outcomes in IBD.

DEFINING MUCOSAL HEALING

MH is usually assessed by ileocolonoscopy or proctosigmoidoscopy in CD and UC, respectively. However, the definition of MH varies across studies and there is no validated definition of MH or endoscopic remission in IBD [7,8]. Various definitions of MH have been used in CD in clinical trials and referral center-based studies (Table 1 and 2) : absence of mucosal ulcerations and ulcers [9,10] or absence of ulcerations at follow-up endoscopy in patients who had ulcerations present at baseline ileocolonoscopy [11]. Definition of MH in CD as the total disappearance of ulcers is simple in clinical practice, but this binary statement does not take into account patients with evidence of MH under treatment with few lesions left such as erosions. In UC, the International Organization of IBD made a consensus in 2007 to define MH : absence of friability, blood, erosions and ulcers in all visualized segments of the

gut mucosa [12]. Presence of only abnormal vascular pattern is still compatible with MH according to panel experts [12].

For the assessment of MH, clinicians require reproducible and validated scoring indices of disease activity (Table 1) [12]. There are mainly three endoscopic disease activity indexes used in clinical trials for CD: the Crohn's Disease Endoscopic Index of Severity (CDEIS) [13], the Simple Endoscopic Score for Crohn's Disease (SES-CD) [14] and the Rutgeerts score [15]. The CDEIS is a prospectively built scoring index, based on elementary CD lesions and percentage of involvement of different ileocolonic segments [13]. The CDEIS, considered as the gold standard scoring index, is regarded as complex and this limits its usefulness in clinical practice, with use largely restricted to the clinical trial setting. A simple index, the SES-CD has been developed and correlates well with the CDEIS [14]. SES-CD involves four variables: ulcer sizes, the extent of ulcerated surface, extend of affected surface and stenosis in five segments bowel. However, the SES-CD is not validated. For both indices, there is no validated cut-off value for defining endoscopic remission, response or MH. Two cut-offs defining endoscopic remission (CDEIS <6) and complete MH (CDEIS <4) have been proposed [16].

The Rutgeerts score is used in the postoperative setting to determine the presence and severity of endoscopic disease recurrence in the neoterminal ileum after ileal or ileocolonic resection [9]. Scoring is based on the presence of aphthous lesions, inflamed mucosa, nodules, narrowing and ranges from i0 to i4 accordingly [9]. Most of clinical trials have used i2 as cut-off to define endoscopic recurrence. However, the Rutgeerts score still lacks validation.

In the small bowel, capsule endoscopy is increasingly used to assess severity of CD [17]. Specific disease activity indexes have been developed, but still await validation before using them in clinical trials and/or clinical practice [18].

In UC, the first index was developed by Truelove and Witts in a placebo-controlled trial on cortisone treatment [19]. Thereafter, several endoscopic system scoring systems have been developed (modified Baron score [20], Mayo endoscopic subscore [21]...) but none of them have been fully validated (Table 2). Recently Travis et al. [22] have proposed a new endoscopic score, namely the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Development of this index was made in two phases in order to assess intra- and inter-individual variation in the overall endoscopic assessment of severity [22]. One of the major differences with the Mayo endoscopic subscore is the exclusion of the item “friability” from the endoscopic description of severity [22]. This score is composed of the following items: vascular pattern, bleeding, erosions and ulcers; it should be largely used in clinical trials and clinical practice in the future once validated independently [22].

INDUCTION AND MAINTENANCE OF MUCOSAL HEALING WITH ANTI-TNF AGENTS

Induction

In the ACCENT 1 [23] trial, a randomized controlled trial evaluating the efficacy of infliximab for the treatment of refractory active CD, an endoscopic substudy [10] of 99 patients was performed. MH was observed at week 10 in 29% of patients (13/45) who had received induction therapy with three infusions of infliximab compared with 3% patients (1/29, $p = 0.006$) who received only one infusion at baseline [10]. Systematic maintenance therapy with infliximab therapy every 8 weeks allowed MH in 44% (16/36) of CD patients at weeks 54 compared to 18% (4/22, $p = 0.041$) in patients treated episodically [10]. In the SONIC trial, which compared infliximab, azathioprine monotherapy and combined infliximab

and azathioprine therapy for active luminal CD, MH was significantly higher in the combined arm (44%, $p < 0.001$) at week 26 [24].

The MUSIC trial is an open-label study that assessed the ability of certolizumab pegol to induce MH at 10 weeks in 89 CD patients with active diseases [16]. Induction therapy consisted in subcutaneous injection at weeks 0, 2 and 4 followed by one injection at week 8. At 10 weeks, endoscopic remission (defined as CDEIS < 6) was seen in 42% but MH (defined as absence of ulcers) was seen in only 5% of patients [16]. The EXTEND trial, evaluating the efficacy of adalimumab for the treatment of moderate to severe active ileocolonic CD, has used MH at week 12 as a primary endpoint [9]. 135 CD patients have received 160 then 80 mg induction therapy at weeks 0 and 2, and were then randomized at week 4 to blinded maintenance therapy with 40 mg adalimumab every other week or placebo through week 52. Primary endpoint was achieved in 27% (17/62) of the adalimumab arm compared with 13% (8/61) of placebo-treated patients ($p = 0.056$) [9]. At week 52, rates of MH were 24% and 0, respectively ($p < 0.001$). Remission rates, based on CDEIS, were 52% for adalimumab and 28% for placebo at week 12 ($p = 0.06$) and 28% and 3%, respectively, at week 52 ($p < 0.01$) [9]. (Figure 1)

In the ACT 1 and ACT 2 trials, [25,26] infliximab or placebo were administered intravenously in 364 (in each study) patients with moderate-to-severe refractory UC. Induction therapy with infliximab 5 mg/kg given at weeks 0, 2 and 6 resulted at week 8 in MH in 62% of patients in ACT 1 trial and 60.3% of patients in ACT 2 study compared with 33.9% and 30.9% in the placebo groups of each study ($p < 0.001$ in both trials) [25,26]. A small, open-label study involving 20 patients has evaluated efficacy of adalimumab in patients with endoscopic evidence of moderate to severe active, refractory UC [27]. Induction treatment with adalimumab 160 mg at week 0, 80 mg at week 2 and 40 mg every other week resulted in MH in 30% of patients at week 8 [27]. Finally in the ULTRA 2 trial [28], a

randomized, double-blind, placebo-controlled trial, efficacy of adalimumab in UC patients for induction was evaluated [28]. At week 8, MH was achieved in 41.1% of patients receiving adalimumab and 31.7% of patients receiving placebo ($p = 0.032$) [28]. (Figure 2)

Maintenance

Anti-TNF agents have also demonstrated efficacy in maintaining MH in IBD patients. In the ACCENT 1 trial [23], scheduled treatment strategy with infliximab demonstrated sustained MH in almost 50% of treated patients at 1 year. Moreover, a greater proportion of patients with scheduled treatment achieved complete MH at week 54 compared to the episodic group (50% vs. 7%, $p = 0.007$) [29]. D'Haens et al. [30], demonstrated that early induction therapy with infliximab combined with azathioprine maintenance therapy resulted in a greater rate of MH at 14 weeks (73.1%) compared to the step-up approach with steroids and azathioprine (30.4%, $p = 0.0028$) [30]. In the EXTEND trial, a significant difference was observed in terms of MH at 1 year in the maintenance therapy group with adalimumab compared to the placebo group (24% vs. 0%, respectively) [9]. (Figure 1)

In the postoperative setting, anti-TNF also allows maintenance of MH. In a randomized study, Regueiro et al. studied [24] patients with CD who had undergone ileocolonic resection to receive intravenous infliximab, administered within 4 weeks of surgery and continued for 1 year, or placebo [31]. Rate of recurrence (Rutgeerts score $\geq i2$) at 1 year was significantly lower in the infliximab group (9.1%) compared with the placebo group (84.6%, $p = 0.0006$) [31].

In UC, in the ACT 1 trial scheduled maintenance therapy with infliximab 5 mg/kg every 8 weeks resulted in MH in 45.5% of patients compared with 18.2% ($p < 0.001$) in the placebo group at week 54 [25]. In the ULTRA 2 trial, MH in UC patients under adalimumab

every other week was achieved at week 52 in 25% and 15.4% in the active arm and placebo group, respectively ($p = 0.032$) [28]. (Figure 2)

IMPACT OF MUCOSAL HEALING ON THE DISEASE COURSE

Clinical response/remission

In the ACCENT 1 trial, patients who achieved MH with infliximab had a longer relapse-free than those without MH [32]. Moreover, at week 54, a longer duration of clinical remission was observed in the complete MH group (20 weeks) compared to patients without complete MH (4 weeks) [32]. In a substudy of the ACCENT 1 trial, MH at weeks 10 and 54 was associated with higher clinical remission rates through week 54 although these results were not statistically significant [29].

A substudy of the “step-up/top-down” trial focused on the value of the endoscopic assessment after 2 years of treatment on clinical outcomes at years 3 and 4. MH (defined as a SES-CD score of zero) at 2 years predicted stable sustained clinical remission in the following 2 years in 68% of the patients versus 35% of patients ($p = 0.004$) with endoscopic evidence of persistent disease activity (defined as a SES-CD score from 2 to 9) [33]. In a large retrospective cohort study involving 214 CD patients under anti-TNF therapy, Schnitzler et al. evaluated the impact of MH on long-term outcomes [11]. At 5 years, clinical remission was maintained in 65% (83/128) of patients with MH compared with 40% (34/86) of patients who did not achieve MH ($p = 0.0004$) [11].

Rutgeerts score has become the gold standard to evaluate CD postoperative recurrence as severity of endoscopic lesions at 1 year has been demonstrated to be predictive of clinical recurrence [15]. A total of 89 CD patients who had been treated by ileal resection were

included in a prospective cohort study [15]. Three years after surgery, the endoscopic recurrence rate was 85% and symptomatic recurrence occurred in 34% [15]. Endoscopic disease often recurs after infliximab is stopped. In a prospective cohort study of 12 consecutive patients under postoperative infliximab regimen, treatment was stopped 3 years after surgery. Discontinuation of infliximab resulted in endoscopic recurrence at 4 months in 10 of 12 patients (83%) [34].

In UC, similar findings were reported in a landmark study from 1966 [35]. Indeed 40% of UC patients who achieved MH after acute treatment with oral and rectal corticosteroids remained asymptomatic during a 1-year follow up [35], whereas only 18% of patients who did not achieve MH after treatment remained asymptomatic during the same period [35]. In the ACT 1 and ACT 2 trials [25,26], the proportion of patients in clinical remission at week 30 of therapy was fourfold greater for patients with MH at week 8 (48.3% vs. 9.5%, respectively).

Overall, these findings suggest that MH is associated with both higher clinical response and lower relapse rates in both CD and UC [36].

Hospitalizations

In the endoscopic substudy of the ACCENT I trial, patients achieving MH at both weeks 10 and 54 needed less CD-related hospitalizations (0%) compared to those with MH at only one of both visits (18.8%) or with no healing at either visit (28%) [29]. In a retrospective single centre cohort study evaluating the long-term outcome of infliximab in 214 patients with CD, patients who achieved MH needed hospitalization less frequently compared to patients who did not (42.2% vs. 59.3%, respectively, $p = 0.0018$) [11].

In UC, Ardizzone et al. showed that no MH after first course of corticosteroid therapy was associated with a more aggressive disease course [37]. 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; $P = 0.0029$) [37].

Thus, MH is associated with lower hospitalization rates in both UC and CD [36].

Surgery

Extensive and deep ulcerations in CD patients predicted a more aggressive clinical course with increased rates of penetrating complications and surgery [38]. In a retrospective single center cohort study, Schnitzler et al. found that patients who had MH under infliximab regimen needed less abdominal surgeries than those who did not achieve MH (14.1% [12/89] vs. 38.4% [33/86], respectively, $P < 0.0001$) [11]. In a Norwegian population-based cohort study involving 458 IBD patients a greater proportion of CD patients (11% [6/53]) who achieved MH at 1 year were able to avoid surgical resection by 5 years compared with 20% (18/88) of patients without MH at 1 year ($p = 0.10$) [39]. Regarding UC, 2% of patients with MH at 1 year needed a surgical resection by 5 years compared to 7% of patients without MH ($p = 0.02$) [39].

In a retrospective single center study, Ferrante et al. [40] demonstrated that a longer colectomy-free survival was observed among UC patients who achieved MH (defined as Mayo endoscopic subscore of 0 or 1) at week 4 or 10.

Hence, MH is associated with a reduced need for surgery in both CD and UC [36].

Colorectal cancer

In a case-control study of 68 UC patients and 136 matched controls, histological inflammation score was the only independent risk factor for the development of colorectal neoplasia (OR 4.69, 95% CI, 2.10-10.48; $P < 0.001$) [41].

In a subsequent study, the same authors showed that macroscopically normal endoscopic findings returned the 5-year cancer risk to that of the general population (OR 0.38, 95% CI, 0.19-0.73; $P = 0.003$) [42]. Rubin et al. also demonstrated a higher risk of cancer and dysplasia in UC patients with a higher inflammatory activity score (OR 2.73, 95% CI, 1.44-5.18; $P = 0.002$) [43]. Gupta et al. confirmed that histological inflammation over time was associated with the progression towards advanced neoplasia in UC (Hazard ratio 3, 95% CI, 1.4-6.3) [44].

MH is thus associated with a lower risk of colorectal cancer in UC, whereas such data are lacking in CD [36].

CONCLUSION

The definition of MH is still debated and no formal definition has been universally accepted. Except for CDEIS, all endoscopic indexes are still lacking validation in CD and UC. Anti-TNF therapy is the most potent drug class to induce and maintain MH in IBD. MH may change the natural course of the disease by decreasing the need for surgery and reducing hospitalization rates in both UC and CD. Mucosal healing may also prevent the development of long-term disease complications, such as bowel damage in CD and colorectal cancer in UC. Schnitzler et al. [11] have shown that MH predicts long-term outcome with maintenance therapy with infliximab in CD. 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). Hence, the degree of MH that is required to change the disease course will require further investigation.

Table 1. Main clinical trials with anti-TNF agents using mucosal healing (MH) as a primary or secondary endpoint in CD.

Study name (Ref.)	Study design	Anti-TNF agent	Endoscopic index used	MH definition
ACCENT 1 endoscopic substudy [10]	Multicenter, randomized, doubleblind controlled study	Infliximab	CDEIS	Complete absence of mucosal ulcerations that were observed at baseline
SONIC [24]	Multicenter, randomized, double blind controlled study	Infliximab	No score used; only descriptive evaluation	Complete absence of mucosal ulceration in the colon and terminal ileum
D’Haens et al. [30]	Multicenter, open- label, randomized study	Infliximab	SES-CD	No ulcers
MUSIC [16]	Multicenter, open- label study	Certolizumab	CDEIS	Absence of ulcers Endoscopic remission defined as CDEIS < 6
EXTEND [9]	Randomized, double blind, placebo-controlled study	Adalimumab	SES-CD	Absence of mucosal ulceration

Table 2. Main clinical trials with anti-TNF agents using mucosal healing (MH) as a secondary endpoint in UC.

Study name (Ref.)	Study design	Anti-TNF agent	Endoscopic index used	MH definition
ACT 1 [25]	Multicenter, randomized, double-blind, placebo-controlled study	Infliximab	Mayo endoscopic subscore	Absolute subscore for endoscopy of 0 or 1
Afif et al. [27]	Multicenter, open- label study	Adalimumab	Mayo endoscopic subscore	Decrease in endoscopic subscore from 2 or 3 at baseline to 0 or 1
ULTRA 2 [28]	Multicenter, randomized, double-blind, placebo-controlled trial	Adalimumab	Mayo endoscopic subscore	Endoscopy subscore 0 or 1

Figure 1. Number of CD patients achieving MH (%) in clinical trials with anti-TNF agents.

Figure 2. Number of UC patients achieving MH (%) in clinical trials with anti-TNF agents.

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