Mucosal Healing in Crohn's Disease: Bull's Eye or Bust? "The Pro Position"

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Keywords

Crohn's disease · Disease assessment · Treatment targets · Clinical remission · Mucosal healing

Abstract

Background: Crohn's disease (CD) is a chronic inflammatory disorder affecting the gastrointestinal tract with disease behaviour based on the depth and severity of mucosal injury. Cumulative injury can result in complications including stricture formation and penetrating complications which often require surgical resection of diseased segments of the intestine resulting in significant morbidity. Accurate assessment of disease activity and appropriate treatment is essential in preventing complications. **Summary:** Treatment targets in the management of CD have evolved with the advent of more potent immunosuppressive therapy. Targeting the resolution of sub-clinical inflammation and achieving mucosal healing is associated with the prevention of stricturing and penetrating complications. Identifying non-invasive modalities to assess mucosal healing remains a challenge. **Key Messages:** Mucosal healing minimizes the risk of developing disease complications, prolongs steroid-free survival, and reduces hospitalization and the need for surgical intervention.

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Introduction

Crohn's disease (CD) is a chronic inflammatory disorder affecting the gastrointestinal tract. Different disease behaviours have been described based on the depth and severity of mucosal injury. Cumulative injury due to unchecked inflammation results in complications including stricture formation and penetrating complications, leading to abscess and fistula development. These complications often require surgical resection of diseased segments of the intestine. The aetiology of CD is unclear but involves a complex interplay of host genetic, microbiome, and environmental factors. As no curative therapy is currently available, the aim of CD treatment is focused on inducing and maintaining disease remission to reduce progressive bowel damage [1]. Increasingly potent anti-inflammatory and immunosuppressant therapies have been employed to control disease and prevent progression. Several different inflammatory cytokine pathways have been implicated resulting in targeted biological therapies. Treatment targets in CD have evolved with the development of these increasingly successful and complex therapeutic modalities (Table 1). The traditional targets of symptom control and normalization of inflammatory markers are no longer acceptable targets as these have not

Table 1. Treatment targets in Crohn's disease [7, 17, 20, 21, 31–34, 36]

Author	Measurement	Treatment target
Hanauer et al. [31, 32]	CDAI <150	Clinical remission (weeks 4–52)
Schopfer et al. [17]	FCP <70 µg/g	Mucosal healing
Boschetti et al. [20]	FCP 82–168 µg/g	Clinical remission (weeks 12–12)
Guidi et al. [21]		
Lin et al. [36]	FCP 50–250 µg/g	Clinical remission
Colombel et al. [7]	CDEIS <4	Mucosal healing (week 48)
	Absence of deep ulcers	
Danese et al. [33]	Reduction in SES-CD ≥50%	Mucosal healing (week 48)
Yzet et al. [34]	CDEIS=0	Complete mucosal healing
	CDEIS 1–4	Partial mucosal healing

CDAI, Crohn's Disease Activity Index; FCP, faecal calprotectin; CDEIS, Crohn's Disease Endoscopic Index of Severity; SES-CD, Simple Endoscopic Score for Crohn's Disease.

been shown to prevent disease progression. With the development of targeted biological therapies, therapeutic goals and endpoints have shifted towards achieving resolution of mucosal inflammation and ulceration, thereby minimizing the development of disease complication and reducing hospitalization and need for surgical intervention. A “treat-to-target” approach has been increasingly supported, with the target moving beyond clinical response or remission to focus sharply on endoscopic response [2]. There is an increasing body of evidence to suggest a more profound disease remission and normalization of intestinal function when mucosal healing is achieved. Nonetheless, accurate assessment of intestinal healing beyond direct endoscopic visualization remains a challenge, and some remain sceptical that the risk of treatment toxicity and costs involved in achieving such targets outweigh the benefits and do not necessarily alter the natural history of the disease. We will review the components of disease monitoring in CD including clinical, biochemical, and endoscopic assessment and then present the evidence for mucosal healing as the optimal treatment target to prevent cumulative bowel damage and subsequent surgical resection.

Clinical Remission

The initial treatment of CD involved non-selective systemic immunosuppression with treatment success monitored largely by clinical symptoms (and simple blood markers of inflammation in some cases). It became evident however that by achieving clinical remission alone, there was no impact on disease course prevention of com-

plications or rates of surgical intervention [3]. Clinical disease activity indices including the Harvey-Bradshaw Index (HBI) and the Crohn's Disease Activity Index (CDAI), which focus mainly on clinical signs and symptoms, provide simple assessment tools for the clinical setting. While symptom relief is important for patients and correlates with improved quality of life as measured by patient-reported outcomes, it is an insufficient treatment target in isolation. Clinical symptoms alone correlate poorly with the extent of mucosal inflammation in CD [4, 5] and may indeed overestimate the extent of disease activity [6]. Furthermore, the CALM study demonstrated that treatment escalation guided by symptoms alone does not result in corresponding endoscopic healing [7]. Indeed, a significant number of patients who achieve clinical remission will have persistent endoscopic activity on assessment [4].

Non-Invasive Assessment of Mucosal Healing

Non-invasive biomarkers of inflammation including C-reactive protein (CRP) and faecal calprotectin (FCP) have been employed to detect disease activity with varying success across studies [8, 9]. The addition of these objective biomarkers of inflammation to clinical symptoms to create a composite assessment tool improves the sensitivity in detecting endoscopic disease activity [10]. CRP correlates well with severe endoscopic activity and treatment response to biologic therapy [11, 12], however is less sensitive for mild to moderate disease activity [13]. While there is an association between low CRP values and reduced risk of clinical relapse [14], a normal CRP does not exclude endoscopic activity as ap-

Table 2. Persistent endoscopic activity has adverse clinical impact [25–27, 37–39]

Author	Parameter	Statistical analysis	p value
Click et al. [25]	Elevated CRP increases the risk of hospitalization	Adjusted HR 2.12 (95% CI: 1.13–3.98)	0.02
Baert et al. [27]	Increased steroid requirement with endoscopic activity (SES $\geq$ 1)	Adjusted HR 4.35 (95% CI: 1.1–17.2)	0.04
Ungaro et al. [26]	Deep remission reduces disease progression	Adjusted HR 0.19 (95% CI: 0.07–0.31)	0.01
Colombel et al. [37]	Normalization of CRP and MH with combination therapy at week 26	OR 4.83 (95% CI: 2.11–11.03)	0.059
Ferrante et al. [38]	MH at week 26 associated with steroid-free remission at week 50	AUC 0.606 (95% CI: 0.532–0.680)	0.061
Kiss et al. [39]	CRP <10 mg/L at week 12 associated with endoscopic response at week 52	OR 6.84 (95% CI: 2.34–20.0)	<0.001

CRP, C-reactive protein; MH, mucosal healing.

proximately 20–30% of patients do not mount a CRP response [13]. Therefore, it cannot be used as a reliable measure of mucosal healing [15]. Indeed, there is no consensus regarding the optimal CRP cutoff to determine disease remission with values of <5 mg/L and <10 mg/L used as targets in various studies. Moreover, as CRP production may itself be inhibited by potent inhibitors of pro-inflammatory cytokines, a CRP decrease may not in fact correlate with healing of the mucosa [8]. FCP has the advantage of increased sensitivity for intestinal inflammation; however, it is not IBD specific. FCP correlates poorly with clinical disease indices but performs better as a measure of endoscopic disease activity correlating closely with endoscopic severity indices [16, 17], with a sensitivity of 82% in detecting endoscopic disease activity [10]. Reductions in FCP following treatment initiation have been associated with improved longer-term outcomes [18], with a persistently elevated FCP following treatment induction increasing the likelihood of subsequent relapse [19]. It is unclear however what threshold of FCP should be targeted, with 1 study demonstrating an accuracy of 87% in detecting endoscopically active disease using a threshold of >70 μ g/g [17], while others found that cutoff values of 82–168 μ g/g at weeks 12–14 following anti-TNF initiation were predictive of clinical remission [20, 21]. Moreover, the authors of the recent STRIDE-II update consider the range of 100–250 μ g/g a grey zone given the low reliability of FCP [22]. The value of FCP as a marker of disease activity applies mainly to colonic and ileocolonic disease with its ability to detect ileal disease significantly reduced [23], limiting its use in CD. Given the ambiguity regarding effective thresholds and its limited reliability beyond the colon, FCP alone cannot be supported as a reliable measure of mucosal healing in CD.

Endoscopic Healing

Disruption to the intestinal barrier function and the subsequent host immune response is a key component of the pathogenesis in CD [24]. Targeting mucosal healing and restoring the normal intestinal mucosal function is therefore more likely to result in better longer-term outcomes. The presence of persistent inflammation whether associated with clinical symptoms or not is associated with a higher risk of hospitalization [25], with frequency of disease exacerbation (many of which require corticosteroid use), and with long-term disease-related complications [26] (Table 2). The resolution of intestinal inflammation and ulceration is therefore an integral component in the success of medical therapies in CD. Ileo-colonoscopy remains the gold standard to assess mucosal healing and allows direct visualization. Several endoscopic scoring systems are used to stratify disease severity including the Crohn's Disease Endoscopic Index of Severity (CDEIS), the Simple Endoscopic Score for Crohn's Disease (SES-CD), and Rutgeerts score. These scoring systems grade the severity of mucosal disease activity based on the presence of erythema, oedema, superficial or deep ulceration, and the extent of mucosal surface involvement either in the native or post-operative bowel. Direct visualization also allows for the detection of complications such as stricture formation and possible therapeutic intervention such as stricture dilatation. However, as an invasive test, its repeated use for serial and dynamic assessment is limited both by patient and capacity factors. Video capsule endoscopy is more acceptable to patients and provides a visual assessment of small bowel mucosa, however is limited by the risk of retention due to stricture formation and is not universally available. The identification of valid biomarkers of disease activity would therefore represent an attractive and acceptable method of disease monitoring. Nonetheless, the currently available

non-invasive serum and faecal biomarkers, while demonstrating modest sensitivity at detecting mucosal inflammation, do not detect the presence of disease complications such as deep ulcers, strictures, or fistulae with any reproducible accuracy. Their use may better lie in identifying patients with persistent sub-clinical disease activity that would benefit from further, more invasive, disease assessment.

Defining Mucosal Healing

Clinical trials of newer biological agents have focused on mucosal healing as a treatment target which, when achieved, has been associated with sustained steroid-free remission, reduced hospitalization and need for surgery, and improved quality of life [27–29]. Despite the shared treatment target, there is no validated definition of mucosal healing in patients with IBD [30], or indeed a consensus regarding how best it should be assessed. Various definitions or descriptions have been employed and used almost interchangeably across studies ranging from partial response, mucosal improvement, and endoscopic remission. There is no consensus regarding the extent of healing necessary to alter the disease course. Whether this entails complete endoscopic resolution of mucosal inflammation and ulceration or rather an improvement from baseline has been debated. Initial clinical trials involving biologic agents assessed drug efficacy in terms of clinical remission, specifically targeting CDAI <150 [31, 32] measured at time points ranging from 4 to 52 weeks but did not identify mucosal healing as a specific target. The SONIC trial was the first to propose mucosal healing as a treatment target, qualified by the resolution of ulceration from baseline to week 26 and demonstrated higher rates of mucosal healing with combination infliximab and azathioprine therapy compared with either as monotherapy [28]. This was the first study to establish the concept of using a combination of immunosuppressive agents in IBD to achieve corticosteroid-free remission and mucosal healing. Following this, the CALM study assessed biologic-naïve patients with active endoscopic CD (CDEIS >6) with treatment escalation with adalimumab based on symptoms alone compared with symptoms and biomarkers combined. The treatment target in the study was mucosal healing defined by a CDEIS score of <4 with the absence of deep ulcers at 48 weeks. This study demonstrated higher rates of mucosal healing in those with timely treatment escalation based on clinical symptoms combined with biomarkers [7]. This evolving “treat-to-

target” therapeutic strategy in CD has been greatly influenced by the management of other chronic inflammatory conditions such as the inflammatory arthropathies, where the concept of early appropriate treatment to prevent higher disease burden and subsequent disability or loss of function is well established. Increasingly, more ambitious therapeutic goals have been targeted in CD involving the resolution of mucosal inflammation and ulceration with the aim of preventing irreversible bowel damage. Most recently, the STARDUST trial, which assessed the efficacy of maintenance ustekinumab using endoscopic response as its primary outcome, defined response by a reduction in SES-CD of $\geq 50\%$ at week 48 from baseline [33]. Interestingly, it found similar rates of endoscopic response in patients treated with ustekinumab maintenance using either a treat-to-target or standard-of-care approach. While there remains uncertainty regarding the optimum target or extent of mucosal healing, treatment strategies in both clinical trials and clinical practice are evolving and supporting the early introduction and escalation of biologic agents aimed at the more comprehensive target of improvement of mucosal injury. One small recent retrospective study with a median follow-up of 4.8 years demonstrated lower rates of treatment failure, less requirements for surgery, and fewer hospitalizations in patients achieving complete mucosal healing (CDEIS = 0) compared with partial healing (CDEIS 1–4) [34].

Conclusion

We now recognize that CD is characterized by progressive bowel damage [35]. There are risks of silent disease progression to structuring and penetrating complications if treatment is based solely on treating symptoms. Biomarkers such as CRP and FCP are useful but lack sensitivity and are therefore best employed as suggested by STRIDE-II as intermediate treatment targets. Ultimately, consensus now favours endoscopic monitoring and the optimization of treatment when feasible to achieve endoscopic mucosal healing. The benefits of achieving this target include reductions in the frequency of disease exacerbations, less corticosteroid use, lower risk of hospitalization, and surgery.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.M. contributed to literature review, interpretation of data, and drafting of the manuscript. J.D. and R.S. contributed to critical review and revising the manuscript. G.D. contributed to concept and design of the study, revising the manuscript, and critical review.

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