Mucosal Healing in Crohn’s Disease: Bull’s Eye or Bust? The “Relative” Con Position

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Abstract

Background: Crohn’s disease is a progressive inflammatory bowel disease. Persistent untreated inflammation can cumulatively result in bowel damage in the form of strictures, fistulas, and fibrosis, which can ultimately result in the need for major abdominal surgery. Mucosal healing has emerged as an attractive, yet ambitious goal in the hope of preventing long-term complications. Summary: Clinical remission is an inadequate measure of disease activity. Noninvasive markers such as fecal calprotectin, CRP, or small bowel ultrasound are useful adjunct tools. However, endoscopic assessment remains the cornerstone in building a treatment plan. Achieving complete mucosal healing has proved to be an elusive goal even in the ideal setting of a clinical trial. Key Messages: Aiming for complete mucosal healing in all patients may result in overuse of medications, higher costs, and potential side effects of aggressive immunosuppressive treatment. More practical goals such as relative or partial healing, for example, 50\% improvement in inflammation and reduction in size of ulcers, ought to be considered, particularly in difficult-to-treat populations.

Introduction

Crohn’s disease (CD) is a progressive inflammatory bowel disease (IBD) that affects any part of the gastrointestinal tract in a patchy distribution with a propensity for the ileocecal region. Persistent untreated inflammation can cumulatively result in bowel damage in the form of strictures, fistulas, and fibrosis which can ultimately result in the need for major abdominal surgery [1]. Preventing such complications is the main goal of a successful therapeutic plan in these patients [2]. Despite advances in treatment of CD, up to 50\% of patients will require surgery within 10 years of diagnosis [3], a stark reminder to clinicians and scientists that more needs to be done in order to change the outlook of this disabling disease. Mucosal healing has emerged as an attractive, yet ambitious goal in the hope of preventing long-term complications. Our objective in this paper is to review mucosal healing as a target of therapy. Specifically, we will discuss complete versus partial endoscopic healing as a current goal in clinical practice and in clinical trials for the management of CD. Should the target, namely endoscopic healing, be relative or complete, customized or universal? Is it practical and achievable and is the prize worth the price?
Illustrative Case

Our patient is a 32-year-old male with moderately severe ileocolonic CD with a history of perianal fistula and abscess (Montreal A1L3B1p) that started 8 years prior to his current presentation. His initial treatment consisted of corticosteroids and azathioprine, which was later escalated to a combination of adalimumab and azathioprine after perianal surgery with drainage of abscess and seton placement. He improved significantly on optimized weekly adalimumab but without achieving clinical remission with a persistently elevated C-reactive protein (CRP). He was switched to infliximab 10 mg/kg plus azathioprine without significant improvement and shortly thereafter developed neutralizing antibodies to infliximab. Ileocolonoscopy showed severely active ileocolonic disease with an SES-CD of 26 (Fig. 1a). He was started on ustekinumab monotherapy ~6 mg/kg, followed by maintenance 90 mg SC every 8 weeks with rapid improvement, clinical remission, and normalization of CRP. Ileocolonoscopy at week 54 showed marked improvement in his ileocolonic disease with an SES-CD score of 10 (Fig. 1b). He remains in steroid-free remission without any hospitalization or surgery over a follow-up period of >4 years.

Evolution of Treatment Outcomes in Crohn’s Disease

Clinical Response and Clinical Remission: Pros and Cons

Symptoms are the first trigger that lead patients to seek care. In CD, these can be insidious and vary based on disease location and phenotype. Abdominal pain and diarrhea are the 2 main symptoms reported by patients with CD [4]. The ease of assessing patients clinically and the weight patients put on improving their symptoms have traditionally made clinical response and remission an attractive goal, both in clinical practice and in the research setting. In an attempt to standardize clinical assessment of patients, the Crohn’s disease activity index (CDAI) was developed in 1976. It has been used over the past 4 decades as a standard tool for the evaluation of clinical disease activity at baseline and during follow-up in clinical trials of CD therapies [5]. Commonly, clinical response is defined based on the degree of decline in the baseline CDAI score by 70–100 points, and clinical remission is confirmed when the CDAI score decreases to below 150. Nonetheless, its use in clinical trials has led to a higher placebo response rate and the need for larger studies. In 2015, the FDA recommended moving away from CDAI [6]. This resulted in the proposal of other scores that are yet to be validated [7, 8]. The use of CDAI in daily clinical
practice is uncommon due to the cumbersome nature of the score and the time it requires to be completed. In routine clinical practice, the Harvey-Bradshaw Index (HBI) seems more practical than CDAI [9]. It is easier to calculate and less prone to recall bias [10]. Data from PRECISE 1 and PRECISE 2 trials showed positive correlation between CDAI and HBI [11].

The disadvantage of using clinical indices as a target for therapy is that they correlate poorly with endoscopic or mucosal healing. In an analysis of the SONIC data, only 50% of patients who were in clinical remission with CDAI <150 had mucosal healing on endoscopy [12]. CDAI tends to be inaccurate in patients with stricturing or penetrating phenotypes. Similarly, HBI has its own limitations. It overestimates disease activity in patients with concurrent functional symptoms [13]. Therefore, while clinical remission remains an important target for therapy, it does not necessarily translate into remission of inflammation. More objective methods of evaluating disease activity have come in favor and have replaced clinical remission as a definitive target of treatment.

Biochemical Markers of Inflammation

As a stool-based inflammatory marker, fecal calprotectin (FC) has proven to be useful in monitoring patients with IBD and in distinguishing IBD from other illnesses with similar clinical presentation [14]. Levels can be affected by disease location, BMI, and concomitant medications [15]. FC has higher correlation with colonic disease compared to isolated ileal CD. Multiple cutoff points have been used to define biochemical remission, but a cutoff value of <274 μg/mg highly predicts CD endoscopic remission (CDEIS <3) with an area under the curve value of 0.925 [16]. Stool-based testing has higher sensitivity to detect inflammation in IBD compared to blood-based markers (88% vs. 48%) [17]. FC is now considered a standard method for monitoring response to therapy in both clinical practice and clinical trials and has been incorporated into the most recent recommendations made by the international organization for inflammatory bowel disease (IOIBD) treat-to-target strategy (STRIDE II) as an intermediate target [18].

Blood-based CRP is one of the most important acute phase proteins in the human body. Due to variability in expressing CRP among patients, the trend in an individual patient is far more important than a particular value. The utility of CRP in clinical management of patients with CD is limited by the fact that one-third of patients with active disease will have normal CRP [19]. Conversely, data from the CALM trial suggest that around 30% of patients with high CRP achieved mucosal healing at week 48. These findings emphasize the point that major therapeutic decisions should take into account other methods of assessment such as endoscopy and not rely solely on CRP [20].

Transmural Healing and beyond

Cross-sectional imaging would be the ideal method of assessment for transmural healing. Some experts have recommended ultrasound as a method for assessing endoscopic healing [21]. While it is an attractive point-of-care method of assessment, ultrasound evaluation lacks a validated scoring method and has a learning curve that led to slow adoption in clinical practices. Moreover, due to the difficulty in achieving this goal with currently available therapies, STRIDE II considered imaging as an adjuvant assessment rather than a target for therapy [18]. The more desirable, and more difficult, target to achieve is histological healing. Real-world data indicate that <15% of CD patients achieve this target with anti-TNF agents [22]. Nevertheless, transmural healing continues to gain popularity as a desired treatment outcome.

Endoscopic Healing

Endoscopic evaluation of the digestive canal remains the cornerstone for making the diagnosis of CD and allows tissue acquisition to exclude alternative diagnoses [1]. The 2 most commonly used validated endoscopic scores for CD are the Crohn's disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for CD (SES-CD). CDEIS evaluates 5 segments of the lower GI tract and describes them based on 4 parameters including type of ulceration and surface involved [23, 24]. A score of <3 indicates remission, higher scores indicate active disease, and a drop of 5 points in the total score indicates response to therapy. SES-CD is simpler for use in assessing the 4 segments of the colon and the terminal ileum. These 5 segments are evaluated in terms of presence of ulcers, surface covered by ulceration, extent of disease involvement, and the presence of narrowing. An SES-CD score of <2 correlates with remission and a score ≥3 with active disease [23, 25]. A decrease of 50% or more in the total score is considered a response to therapy [26]. Such improvement in SES-CD at 26 weeks after starting therapy has been shown to predict corticosteroid-free remission at 50 weeks with a sensitivity of 74% and a specificity of 48% [27, 28]. In a study of central readers, SES-CD had a higher interrater and intrarater reliability compared to CDEIS with an ICC of 0.83 (0.75–0.88) and 0.91 (0.89–0.95), respectively [29]. Although SES-CD has...
gained wider acceptance in clinical settings, it is limited by the fact that it underestimates the burden of the disease since it assumes unexamined segments to be free of lesions [27].

Regardless of the scoring method used, performing endoscopic evaluation of the mucosa ≥6 months after starting a biological agent was associated with lower rates of disease-related adverse events and need for corticosteroids [30]. Achieving mucosal healing is associated with improved long-term outcomes including lower risk of surgery, lower rates of relapse, and improved quality of life [31]. Moreover, it is associated with improved disease-related hard outcomes. In an observational study of CD patients receiving infliximab, Schnitzler and colleagues [32] demonstrated that mucosal healing was associated with 50% reduction in need for major abdominal surgeries. Overall, the hospitalization rate was 42.2% among those who achieved mucosal healing compared to 59.3% in those who did not achieve it (p = 0.0018). Interestingly, there was no difference in major abdominal surgeries between those who achieved complete mucosal healing versus those with partial mucosal healing (14.1% vs. 14.0%, respectively). Corticosteroid-free remission rates for up to 4 years after initiation of therapy are significantly higher in patients with mucosal healing compared to those who do not achieve it (70.8% vs. 27.3%, p = 0.036) [33]. On the other hand, lack of mucosal healing predicts complications. In a prospective study of CD patients with clinically quiescent disease undergoing baseline MRE, assessment with video capsule endoscopy, and clinical and biochemical markers at regular intervals, the presence of active disease on video capsule endoscopy, defined as a Lewis score of >350, was the best predictor for a future flare (HR = 10.7, 95% CI: 3.8–30.3; sensitivity 82%; specificity = 77%; PPV = 59%; NPV = 92%) [34].

Clinicians ought to be mindful that the desirable target of complete mucosal healing might not be achievable in all patients. The higher the inflammatory burden in a patient, the less likely they are to achieve complete mucosal healing. The VERSIFY trial prospectively assessed mucosal healing in CD patients receiving vedolizumab. The study population had active disease with a high mean CDAI of 324.2 and a mean SES-CD of 16. More than half the patients had previous TNFi failure. Complete mucosal healing at 26 weeks and 52 weeks did not reach 20% [35]. Similarly, the CALM trial enrolled patients with moderate to severe CD patients who were considered more likely to respond to therapy, consisting of bio-naive patients with a median disease duration of 1 year [36]. Even in the tight control group, where therapy was escalated based on either clinical or biochemical criteria, mucosal healing (CDEIS <4) was achieved in <50% at 48

| Drug         | Author (trial) | N    | Population                      | Mean/median disease duration, years | Time of endoscopic assessment, weeks | Endoscopic endpoint               | Mucosal healing |
|--------------|----------------|------|---------------------------------|------------------------------------|-------------------------------------|-----------------------------------|----------------|
| Infliximab   | Rutgeerts et al. [39] (ACCENT) | 46   | Biologic-naive                  | 7.9                                | 10 and 54                           | Absence of mucosal ulceration     | 31% at week 10 |
| Infliximab   | Colombel et al. [40] (SONIC) | 338  | Biologic-naive                  | 2.3                                | 26                                  | Absence of mucosal ulceration     | 44% azathioprine/infliximab      |
| Adalimumab   | Rutgeerts et al. [41] (EXTEND) | 129  | 51.9% prior TNFi use            | 10.1                               | 12 and 52                           | Absence of mucosal ulceration     | 27% at week 12 |
| Vedolizumab  | Danese et al. [35] (VERSIFY)  | 101  | 54.5% prior TNFi failure        | 11.5                               | 26 and 52                           | Absence of any ulcers, including aphthae | 11.9% at week 26 |
| Ustekinumab  | Danese [38] (STARDUST)*        | 500  | 58.4% failed 1 biologic         | 9.4                                | 16                                  | SES-CD score≤2                    | 11.4%          |
| Adalimumab, Ustekinumab | Sands et al. [37] (SEAVUE)** | 358  | Biologic-naive                  | 2.6                                | 52                                  | SES-CD score≤3                    | 30.7% adalimumab |

* Interim analysis. ** Abstract publication.
weeks [36]. The more aspirational goal of normalization of mucosa with a CDEIS of 0 was achieved in only 18% of patients [36]. Table 1 shows the mucosal healing rates (variably defined) of the pivotal clinical trials in CD. The results highlight the challenge of achieving complete, or near complete, mucosal healing even in the ideal carefully controlled setting of clinical trials and of early disease, as was the case in SONIC and CALM.

**Partial or “Relative” Endoscopic Healing**

A proposed approach for clinical practice is to assess the worst lesions (e.g., large or deep ulcers) which should improve by greater or equal to 50% in cases of response to therapy (a probably more achievable goal is to try to target 50% reduction in inflammation) as is illustrated in the aforementioned clinical case. This has been shown to lead to better outcomes. In a post hoc analysis of 172 patients from the SONIC trial, >50% reduction in SES-CD at 26 weeks predicted steroid-free clinical remission at 50 weeks with a sensitivity of 74% and a specificity of 48% (36–60%) [28]. Similar to SES-CD, signature lesions should improve in at least one aspect; for example, large ulcers should decrease in size and small ulcers should heal completely [42]. Furthermore, data from the REACT trial demonstrated a significant reduction in a very important composite endpoint of hospitalizations and surgery in the combination therapy arm based only on clinical assessment (clinical remission using the HBI) [43]. This argues indirectly that hard important endpoints can also be achieved in the absence of full endoscopic healing.

Given the transmural nature of CD, just like clinical remission, mucosal healing does not reflect the full picture of the status of the disease. There are also important pitfalls and remaining questions regarding the concept of mucosal healing and a “blanket” recommendation of complete healing as a target. These include the lack of randomized controlled trials of mucosal healing versus clinical and/or biochemical remission, cost and safety analyses of mucosal healing as an endpoint, convincing asymptomatic patients to escalate therapy, the lack of a standardized definition of endoscopic healing, and arguably the lack of practicality of this strategy in the typical clinical setting. Aiming to fully heal the mucosa can be challenging and might be considered ambitious given the long period it might take to achieve healing and the potential impact a relative improvement might have on disease outcome. Furthermore, based on current recommended guidelines and prevailing dogma, physicians might feel the need to “keep pushing the envelope” when faced with the absence of complete endoscopic healing during follow-up, by either intensifying or changing treatment when such intervention may not be necessary. Importantly, this may result in higher costs and risk of adverse events, as well as rapid and arguably unnecessary cycling of biologics. This can be avoided by personalizing the target and accepting a relative, yet important improvement in mucosal inflammation rather than complete healing with absence of all ulcers.

### Table 2. Failed clinical trials in Crohn’s disease

| Drug               | Mechanism of action                                                | Comments                                                                 |
|--------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------|
| Brodalumab         | Anti-interleukin-17 receptor monoclonal antibody                    | Terminated prematurely because of worsening disease in the treatment arm |
| Vercirnon          | CC chemokine receptor 9 inhibitor                                  | Lack of efficacy and dose-dependent increase in rates of adverse events  |
| Trichuris suis ova | Induction of immune regulatory circuits that impede Th1 and possibly aberrant Th2 responses | Lack of efficacy                                                        |
| Tofacitinib        | JAK inhibition                                                     | Lack of efficacy                                                         |
| Mongersen          | Antisense oligodeoxynucleotide to Smad7                            | Lack of efficacy in the phase 3 trial                                     |
| Abcilumab          | Monoclonal antibody against α4β7                                    | Primary endpoint (clinical remission) at week 8 not met                  |
| Brikakimab         | Anti-IL-12/23 p40 monoclonal antibody                              | Primary endpoint (clinical remission) at week 6 not met                  |
| Amiselimod         | Selective S1P modulator                                            | Lack of efficacy                                                         |
| PF-00547659 (SHP647)| Monoclonal antibody to MAdCAM                                      | Lack of efficacy at weeks 8 and 12                                       |
Practical Concerns with Current Therapies: Safety and Efficacy

Despite their widespread use in immune-mediated diseases, monoclonal antibody therapy can lead to adverse events. Observational data and population-based studies suggest that TNFi use in IBD is associated with 1.5–2 times higher risk of serious infections compared to conventional therapy [44]. The TREAT registry looked at patients receiving infliximab for moderate to severe CD with a follow-up period of 13 years. The rate of serious infections was 2.2 events per 100 person-years (PY) in infliximab-treated patients compared with 0.9 of 100-PY in patients treated with other therapies [45]. Serious infections were also reported at a rate of 4.7 events per 100-PY from 556 patients (11.1%) treated with adalimumab in the PYRAMID registry [46]. Admittedly, the risks of such adverse events are lower with other monoclonal antibodies when used as monotherapy in CD [47].

Apart from safety concerns, cost and access to biological agents remain a challenge for patients and providers. The most common reason for stopping adalimumab among patients who achieved deep remission in the CALM trial was cost and logistical reasons [48]. Even in an ideal situation where access and safety of biological agents are not a concern, limited efficacy remains a reality. As discussed earlier, rates of endoscopic remission (absence of ulcers) with TNFi, vedolizumab, and ustekinumab monotherapy do not exceed 20% [49]. In-tensification of biological therapy may not lead to improved outcomes. In an induction trial of adalimumab in Crohn’s disease (SERENE-CD), intensified dosing regimens were not superior to the standard regimen for achieving clinical and endoscopic endpoints [50].

Although the pipeline of new drugs in CD is promising, breaking the therapeutic ceiling in drug development remains a largely unfulfilled promise, and a number of newer agents continue to fail frustratingly short. One particular disappointment in CD is mongersen. The results of the phase II trial showing a 55–65% persistent clinical remission 3 months after a 14-day course of therapy raised hopes for this anti-SMAD7 agent [51]. Unfortunately, the phase III trial of 700 patients was terminated early due to lack of efficacy [37]. The same medication that resulted in 65% clinical remission rates in the phase II trial led to 22.8% remission rates in the phase III trial, similar to the placebo rate of 25% [52]. Other agents have faced a similar fate, albeit in an earlier phase II stage of development (Table 2). Although the success rate for phase 1 clinical trials for CD exceeds 90%, subsequent phase 2 and 3 studies carry a success rate of only 18% when tracked from start to end, with the success rate of phase 3 trials not exceeding 50% [53]. The above highlights the continued need to properly use and protect our current therapeutic options in CD.

Potential Solutions to Improve Treatment Outcomes in CD

The benefit of partial mucosal healing (debatable definition) should be discussed in the background of the modest therapeutic ceiling associated with our current armamentarium of drugs. The stringent response and remission criteria that are traditionally used to define endoscopic remission such as an SES-CD score <2 or a CDEIS <3 or complete disappearance of previously observed mucosal ulcerations (SES-CD = 0) [54] are probably too lofty given the endoscopic remission rates observed with current effective therapies (Table 1). Potential solutions to this existential therapeutic dilemma include relying on relative targets by comparing response to treatment to baseline values such as used in the STARDUST clinical trial. In this study, a 50% reduction of the SES-CD score from baseline was used as the primary study endpoint. Following 48 weeks of treatment with ustekinumab, 37.7% of patients treated using a treat-to-target approach and 29.9% of patients treated using standard of care approach demonstrated endoscopic remission (p = 0.09). When results were analyzed using last observation carried forward, a statistically significant difference was observed (40.0% vs. 30.8%, p = 0.0494) [38]. Clearly, it would be important to prove that hard clinical endpoints, such as reduced rates of surgery [32] and hospitalization, are achievable in the long term with such a targeted personalized strategy.

Conclusion

The proven short- and long-term benefits of mucosal healing make it an attractive target. Although the argument concerning the precise endoscopic healing target continues, we should perhaps modify our thinking in terms of healing from a strictly dichotomous outcome (“bull’s eye or bust”) to one of healing on an inflammatory continuum unique to every patient (partial or relative healing). Although desirable, complete endoscopic healing is clearly neither achievable nor practical in all patients. Indeed, under the ideal circumstances of a con-
trolled clinical trial, where patients are carefully selected and tightly monitored, mucosal healing rates rarely exceed 50% and complete healing rates rarely exceed 20%. Personalizing both treatment and target is therefore necessary to achieve desirable outcomes. The above notwithstanding a successful strategy remains predicated on proven principles of management in CD including accurate disease characterization and localization, risk stratification, treating early, setting reasonable targets and expectations, monitoring and optimizing at proper intervals, shared decision-making, and multidisciplinary care.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

References

1. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, et al. Crohn’s disease. Nat Rev Dis Primers. 2020;6(1):22.
2. Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology. 2017;152(2):351–e5.
3. Moradkhani A, Beckman LJ, Tabibian JH. Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. J Crohns Colitis. 2013;7(6):667–73.
4. Gemollon F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. Ecco. 3rd European Evidence-based Consensus on the diagnosis and management of Crohn’s disease 2016: part 1: diagnosis and medical management. J Crohns Colitis. 2017;11(1):3–25.
5. Best WR, Becket JM, Singleton JW, Kern F Jr. Development of a Crohn’s disease activity index. National Cooperative Crohn’s Disease Study. Gastroenterology. 1976;70(3):439–44.
6. Dubinsky MC, Collins R, Abreu MT. International Organization for the Study of inflammatory bowel disease. Challenges and opportunities in IBD clinical trial design. Gastroenterology. 2021;161(2):400–4.
7. Higgins PDR, Harding G, Leidy NK, DeBusk R, Patrick DL, Viswanathan HN, et al. Development and validation of the Crohn’s disease patient-reported outcomes signs and symptoms (CD-PRO/SS) diary. J Patient Rep Outcomes. 2017;2(1):24.
8. Dulai PS, Jairath V, Khanna R, Ma C, McCarrrier KP, Martin ML, et al. Development of the Crohn’s disease and ulcerative colitis. Aliment Pharmacol Ther. 2020;51(11):1047–66.
9. Harvey RF, Bradshaw JM. A simple index of Crohn’s disease activity. Lancet. 1980;1(8167):514.
10. Best WR. Predicting the Crohn’s disease activity index from the Harvey-Bradshaw Index. Inflamm Bowel Dis. 2006;12(4):304–10.
11. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn’s disease activity and Harvey-Bradshaw indices in assessing Crohn’s disease severity. Clin Gastroenterol Hepatol. 2010;8(4):357–63.
12. Peyrin-Biroulet L, Reinisch W, Colombel JF, Mantzaris GJ, Kornbluth A, Diamond R, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn’s disease: the SONIC trial. Gut. 2014;63(1):88–95.
13. Sturm A, Maaser C, Calabrese E, Annese V, Fiorino G, Kucharzik T, et al. Ecco-ESGAR Guidelines for diagnostic assessment in IBD part 2: IBD scores and general principles and technical aspects. J Crohns Colitis. 2019;13(3):273–84.
14. Arasaradnam RP, Brown S, Forbes A, Fox MR, Hungin P, Kelman L, et al. Guidelines for the investigation of chronic diarrhoea in adults: British Society of gastroenterology, 3rd edition. Gut. 2018;67(8):1380–99.
15. Dai C, Jiang M, Sun MJ. Monitoring a combination of calprotectin and infliximab identifies patients with mucosal healing of Crohn’s disease. Clin Gastroenterol Hepatol. 2020;18(1):262.
16. Lobaton T, Lopez-Garcia A, Rodriguez-Moranta F, Ruiz A, Rodriguez L, Guardiola J. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn’s disease. J Crohns Colitis. 2013;7(12):e691–51.
17. Mosli MH, Zou G, Garg SK, Feagan BG, MacDonald JK, Chande N, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. Am J Gastroenterol. 2015;110(6):802–20; quiz 20.
18. Turner D, Ricciuto A, Lewis A, D’Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2021;160(5):1570–83.
19. Boirivant M, Leoni M, Tariciotti D, Fais S, Squarcia O, Pallone F. The clinical significance of serum C reactive protein levels in Crohn’s disease. Results of a prospective longitudinal study. J Clin Gastroenterol. 1988;10(4):401–5.
20. Reinisch W, Panaccione R, Bossuyt P, Baert F, Armuza I, Hebuterne X, et al. Association of biomarker cutoffs and endoscopic outcomes in Crohn’s disease: A post hoc analysis from the CALM Study. Inflamm Bowel Dis. 2020;26(10):1562–71.
21. Bonnaud G, Bouhnik Y, Hagehe H, Hebuterne X, Pariente B, Robin X, et al. Monitoring of inflammatory bowel disease in 2019: a French consensus for clinical practice. Dig Liver Dis. 2020;52(7):704–20.
22. Tursi A, Elisei W, Picchio M, Penna A, Lecca PG, Forni G, et al. Effectiveness and safety of infliximab and adalimumab for ambulatory Crohn’s disease patients in primary gastroenterology centres. Eur J Intern Med. 2014;25(5):485–90.
23. White JR, Jairath V, Moran GW. Evolution of treatment targets in Crohn’s disease. Best Pract Res Clin Gastroenterol. 2019;33:38–39; 101599.

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Mahmoud Mosli has contributed to the conception, drafting the manuscript, revising the manuscript critically for important intellectual content, and final approval of the version to be published and has agreed to be accountable for all aspects of the work. Turki Alameel has contributed to the conception, drafting the manuscript, revising the manuscript critically for important intellectual content, and final approval of the version to be published and has agreed to be accountable for all aspects of the work. Ala Sharara has contributed to the conception, drafting the manuscript, revising the manuscript critically for important intellectual content, and final approval of the version to be published and has agreed to be accountable for all aspects of the work.

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24 Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn’s disease: a prospective multicentre study. Groupe d’Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;30(7):983–9.

25 Daperno M, D’Haens G, Van Assche G, Baert F, Buleis P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn’s disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505–12.

26 Vuitton L, Marteau P, Sandborn WJ, Levesque BG, Feagan B, Vermeire S, et al. IOBD technical review on endoscopic indices for Crohn’s disease clinical trials. Gut. 2016;65(9):1447–55.

27 Al-Bawardy B, Hansel SL, Fidler JL, Barlow JM, Bruining DH. Endoscopic and radiographic assessment of Crohn’s disease. Gastroenterol Clin North Am. 2017;46(3):493–513.

28 Ferrante M, Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, et al. International Organization for the Study of Inflammatory Bowel Disease. Validation of endoscopic activity scores in patients with Crohn’s disease based on a post hoc analysis of data from SONIC. Gastroenterology. 2013;145(5):978–86.

29 Khanna R, Zou G, D’Haens G, Rutgeerts P, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn’s disease. N Engl J Med. 2010 Apr 2;362(15):1383–95.

30 Schnitzler F, Fidder H, Ferrante M, Noman M, Arijis J, Van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn’s disease. Inflamm Bowel Dis. 2020;25(11):1828–37.

31 Bernstein CN, Hitchon CA, Wallis R, Bolton JM, Sareen J, Walker JR, et al. Burden CTiD, managing the effects of psychosocial comorbidity in chronic inflammatory disease. Inflamm Bowel Dis. 2019;25(2):360–8.

32 Schnitzler F, Fidder H, Ferrante M, Noman M, Arijis J, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn’s disease. Gastroenterology. 2010;138(2):463–1; quiz e10–1.

33 Ben-Horin S, Lahat A, Amitai MM, Klang E, Yablecovitch D, Neuman S, et al. Assessment of small bowel mucosal healing by video capsule endoscopy for the prediction of short-term and long-term risk of Crohn’s disease flare: a prospective cohort study. Lancet Gastroenterol Hepatol. 2019;4(7):519–28.

34 Danese S, Sandborn WJ, Colombel JF, Vermeire S, Glover SC, Rimola J, et al. Endoscopic, radiologic, and histologic healing with vedoluzumab in patients with active Crohn’s disease. Gastroenterology. 2019;157(4):1007–18.

35 Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vanäksee T, et al. Effect of tight control management on Crohn’s disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2017;390(10114):2779–89.

36 Sands BE, Feagan BG, Sandborn WJ, Schreiber S, Peyrin-Biroulet L, Fréderic Colombel J, et al. Mongersen (GED-0301) for active Crohn’s disease: results of a Phase 3 Study. Am J Gastroenterol. 2020;115(5):738–45.

37 Sands BE, Feagan BG, Sandborn WJ, Schreiber S, Peyrin-Biroulet L, Fréderic Colombel J, et al. Mongersen (GED-0301) for active Crohn’s disease: data from 5 randomized controlled induction trials. Clin Gastroenterol Hepatol. 2020;18(5):1121–32.

38 Danese S. Clinical and endoscopic response to treat-to-target versus standard of care in Crohn’s disease patients treated with Ustekinumab: week 48 results of the STAR-DUST trial. United European Gastroenterol J. 2020;8(Suppl 1). abstract LB11.

39 Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn’s disease. Gastrointest Endosc. 2006;Mar;63(3):433–42; quiz 464.

40 Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D’Haens G, Diamond RH, Brousard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn’s disease. N Engl J Med. 2010 Apr 13;362(15):1383–95.

41 Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn’s disease: data from the EXTEND trial. Gastroenterology. 2012 May;142(5):1102–1111.e2.

42 Reinisch W, Gecse K, Halfvarson J, Irving PM, Jahnson S, Peyrin-Biroulet L, et al. Clinical practice of adalimumab and infliximab biosimilar treatment in adult patients with Crohn’s disease. Inflamm Bowel Dis. 2021;27(1):106–22.

43 Khanna R, Bressler B, Levesque BG, Zou G, Stitt LW, Greenberg GR, et al. Early combined immunosuppression for the management of Crohn’s disease (REACT): a cluster randomised controlled trial. Lancet. 2015;386(10006):1825–34.

44 Holmer A, Singh S. Overall and comparative safety of biologic and immunosuppressive therapy in inflammatory bowel diseases. Expert Rev Clin Immunol. 2019;15(9):969–79.

45 Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with Crohn’s disease: more than 5 years of follow-up in the TREAT registry. Am J Gastroenterol. 2012;107(9):1409–22.

46 D’Haens G, Reinisch W, Panaccione R, Satsangi J, Peterssson J, Bereswill M, et al. Lymphoma risk and overall safety profile of adalimumab in patients with Crohn’s disease with up to 6 years of follow-up in the pyramid registry. Am J Gastroenterol. 2018;113(6):872–82.

47 Nguyen NH, Singh S, Sandborn WJ, Positioning therapies in the management of Crohn’s disease. Clin Gastroenterol Hepatol. 2020;18(6):1288–97.

48 Ungaro RC, Yzet C, Bossuyt P, Baert FJ, Vanäksee T, D’Haens GR, et al. Deep remission at 1 year predicts progression of early Crohn’s disease. Gastroenterology. 2020;159(1):139–47.

49 Duijvestein M, Jeyarajah J, Guzzetti L, Zou G, Parker CE, van Viegten T, et al. Response to placebo, measured by endoscopic evaluation of Crohn’s disease activity, in a pooled analysis of data from 5 randomized controlled induction trials. Clin Gastroenterol Hepatol. 2018;15(1):1121–32.

50 D’Haens G, Sandborn W, Loftus E, Hanauer S, Schreiber S, Laurent Peyrin-Biroulet L, et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active Crohn’s disease: results from the SERENE-CD induction study. United European Gastroenterol J. 2019;7.

51 Monteleone G, Neurath MF, Ardizzoni S, Di Sabatino A, Fantini MC, Castiglione F, et al. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn’s disease. N Engl J Med. 2015;372(12):1104–13.

52 Blura M, Lichtenstein GR, Mongersen and SMAD-7 inhibition, not a lucky 7 for patients with IBD: when trial design is as important as disease therapy. Am J Gastroenterol. 2020;115(5):687–8.

53 Parker JL, Clare Kohler J. The success rate of new drug development in clinical trials: Crohn’s disease. J Pharm Pharm Sci. 2010;13(2):191–7.

54 Pironet de Chambrun G, Blanc P, Peyrin-Biroulet L. Current evidence supporting mucosal healing and deep remission as important treatment goals for inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2016;10(8):915–27.