

Targeting mucosal healing in Crohn's disease: what the clinician needs to know

Entcho Klenske, Christian Bojarski, Maximilian Waldner, Timo Rath, Markus F. Neurath and Raja Atreya 

Ther Adv Gastroenterol

2019, Vol. 12: 1–11

DOI: 10.1177/
1756284819856865

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Abstract: In recent years, mucosal healing has emerged as a key therapeutic goal in the clinical management of patients with Crohn's disease, as it has been associated with improved long-term clinical outcomes. With the vast improvements in endoscopic imaging techniques and the increase in available treatment options, which reportedly are able to induce mucosal healing, the practising physician is left to wonder: how is endoscopic mucosal healing exactly defined in Crohn's disease, and how can it effectively be achieved and monitored in daily clinical practice? Within this review, we will give an overview of the ongoing debate about the definition of mucosal healing and the modalities to monitor inflammation, and finally present available therapies with the capacity to induce mucosal healing.

Keywords: Crohn's disease, endoscopy, imaging, mucosal healing

Received: 5 March 2019; revised manuscript accepted: 21 May 2019.

Introduction

Crohn's disease (CD) and ulcerative colitis form the two main entities of inflammatory bowel diseases (IBD), which are marked by chronic idiopathic inflammation of the gastrointestinal (GI) tract. Specifically, CD is characterised by transmural inflammation, causing thickening and narrowing of the GI wall and eventually leading to the disabling development of deep ulcerations, fistulae, strictures and abscesses.^{1,2} Furthermore, chronic deep transmural inflammation causes irreversible structural damage and, as in patients with ulcerative colitis, increases the probability of the onset of colitis-associated neoplasia.^{3–5} Within recent years, fostered by several breakthroughs in available medical therapies, therapeutic goals in the treatment of CD have evolved dramatically.

Traditionally, the goals of treatment centered solely on symptom control, before it was recognised that many patients with CD have continued disease activity in the absence of clinical manifestations. Treatment targets have therefore shifted from simply relieving clinical symptoms,⁶ to achieving clinical remission,⁷ steroid free remission,⁸ and finally to achieving mucosal healing,⁹

which may be complemented in the future by transmural healing in cross-sectional imaging techniques and the incorporation of a not-yet-validated histology instrument into the definition of mucosal healing.² The rationale behind this evolution of treatment goals is based on available evidence that mucosal healing is associated with better long-term patient outcome, as defined by reduced risk of relapse, decreased hospitalisation rates, steroid-free remission in follow-up examination,^{6,10,11} and resection free intervals.¹² Specifically, in regard to its direct clinical value, it was shown that patients with CD with mucosal healing have a decreased risk of penetrating complications and probability of surgery as compared with patients with severe ulcerations.¹³ Another clinical benefit is that the presence of mucosal healing in CD is associated with lower rates of major abdominal surgery.¹⁴ Furthermore, patients with mucosal healing have been shown to need less hospitalisation, as compared with patients without mucosal healing.¹⁵ In terms of long-term patient outcome, it was shown that, at 1 year after diagnosis and over the next 7 years, mucosal healing was associated with less inflammation, a decreased need for steroid treatment and a trend

Correspondence to:
Raja Atreya
Department of Medicine
1, Ludwig Demling
Endoscopy Center of
Excellence, Friedrich-
Alexander-University
Erlangen-Nürnberg,
University Ulmenweg 18,
Erlangen, 91054, Germany
Raja.atreya@uk-erlangen.de

Entcho Klenske
Department of Medicine
1, Ludwig Demling
Endoscopy Center of
Excellence, Friedrich-
Alexander-University
Erlangen-Nürnberg,
Germany

Christian Bojarski
Department of
Gastroenterology,
Infectiology and
Rheumatology, Charité
- Universitätsmedizin
Berlin, Berlin, Germany

Maximilian Waldner
Timo Rath
Markus F. Neurath
Department of Medicine
1, Ludwig Demling
Endoscopy Center of
Excellence, Friedrich-
Alexander-University
Erlangen-Nürnberg,
Germany

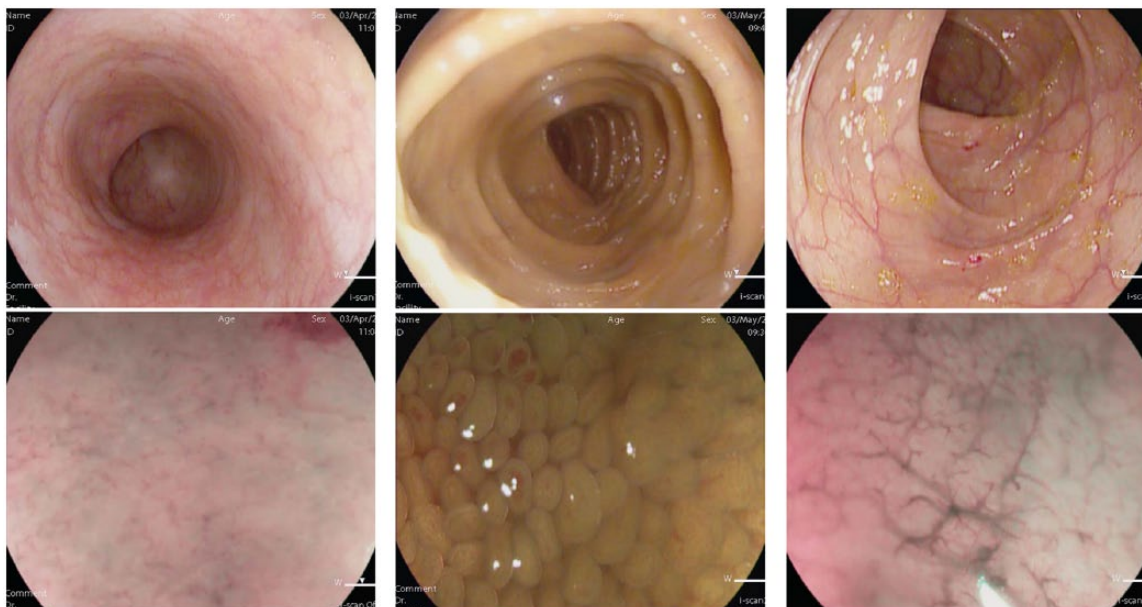


Figure 1. Examples of microinflammation under magnification endoscopy with i-scan optical enhancement (OE). Upper row: ileal/colonic segments with no sign of inflammation under standard high definition white light endoscopy (HD-WLE). Lower row: same gastrointestinal (GI)-segments show signs of microinflammation under magnification endoscopy with i-scan OE.

towards lower resection rates.¹² Furthermore, the long-term follow-up of patients who achieved complete mucosal healing at 2 years had a higher rate of clinical remission, steroid-free remission, and steroid-free remission without flares through years 3 and 4.⁹ These are important findings for the patient, as they substantially influence a good level of quality of life.

Mucosal healing is often also used as a key parameter when considering stopping or de-escalating ongoing biological treatment to reduce the risk of side effects and pharmacoeconomic costs. Patients with mucosal healing, in combination with clinical and biomarker remission, were shown to have a higher probability of remaining disease-free than patients with persisting mucosal inflammation.¹⁶ With a more profound understanding of the underlying etiopathology of IBD, novel classes of drugs with different mechanisms of action have been introduced into clinical practice, replacing the prolonged use of corticosteroids in the treatment of patients with CD.¹⁷ These advances in CD therapeutics, which began with the arrival of monoclonal antibodies targeting tumour necrosis factor (TNF), have enabled us to achieve mucosal healing at a meaningful level to ensure optimal disease control and less progression of tissue damage. Moreover,

recent technical advancements in endoscopy allow a more precise assessment of mucosal and vascular features, facilitating precise recognition of mucosal healing during follow-up endoscopy, which goes beyond data obtainable with white light endoscopes. With advances in optical and digital enhancement in available endoscopic systems, subtle mucosal changes indicative of persisting inflammation can now be recognised in formerly noninflamed tissue (Figure 1).

This review shall give an overview of the parameters that demarcate mucosal healing (highlighting the current lack of an objective, generally accepted definition), the imaging methods of monitoring mucosal healing following inflammation and, finally, therapies enabling us to achieve this important therapeutic outcome in patients with CD.

The difficulty in defining mucosal healing

Mucosal healing, which can be regarded as restitution of the intestinal lining, is generally defined as regression or disappearance of endoscopic lesions in CD. In order to evaluate the presence or absence of mucosal healing, various endoscopic scoring indices have been developed. The most

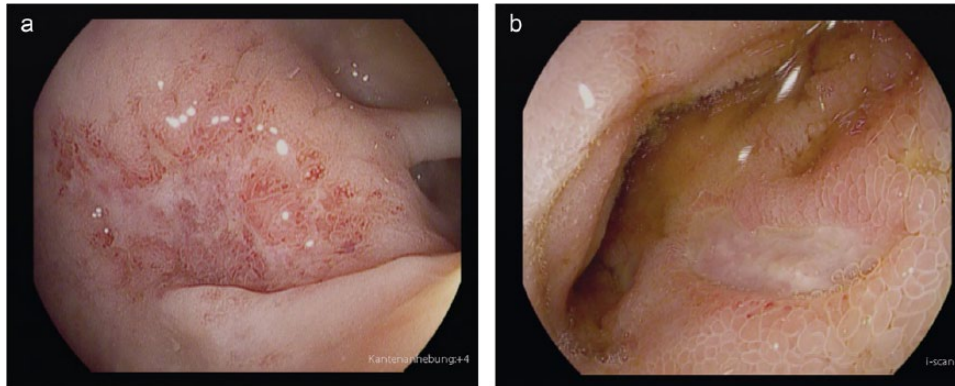


Figure 2. Examples of ulcerations in Crohn's disease. (a) Superficial ulceration in a CD patient. (b) Deep ulceration in a CD patient.

common ones are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD).

The first attempt to quantify inflammation was done as early as 1989 when the CDEIS was introduced.¹⁸ The CDEIS scores the presence of superficial ulcerations (Figure 2a), deep ulcerations (Figure 2b), surface involved with disease, and of surface involved with ulcerations in five segments (rectum, sigmoid and left colon, transverse colon, right colon, and ileum). The respective scores for each item are summed, then divided by the number of evaluated segments. Presence of ulcerated or nonulcerated stenosis leads to the addition of points. The range of the CDEIS is 0 (no evidence of activity) to 44 (deep ulcerations present in all surfaces). As application of the CDEIS is regarded as cumbersome and time consuming, the supposedly simpler SES-CD was introduced.¹⁹ It is a less complex instrument that reduced interobserver variation and the number of calculations. The SES-CD is scored based on four endoscopic variables (area of affected surface, presence and size of ulcers, extent of ulcerated surface, and presence of stenoses) in the five intestinal segments mentioned above. The total SES-CD score range is 0–60, with each section ranging from 0 to 12 points. To evaluate the intrarater and interrater reliability of these indices, endoscopic assessments of 50 colonoscopies between four central readers were analysed. There was a near perfect correlation between the SES-CD and the CDEIS, with a correlation coefficient of $r=0.938$ ($p<0.0001$).²⁰ Intrarater reliability for CDEIS and SES-CD was very good (95% CIs), with intraclass correlation coefficients

of 0.89 (0.86–0.93) and 0.91 (0.89–0.95), respectively. The most common sources of disagreement were interpretation of superficial ulceration, definition of disease site at the ileocolonic anastomosis, assessment of anorectal lesions and grading severity of stenosis.²¹

Recently, responsiveness of the CDEIS and SES-CD to treatment with the anti-TNF antibody adalimumab was evaluated. Here, the SES-CD demonstrated a stronger correlation with the global endoscopic evaluation of severity compared with the CDEIS.²² The main limitation of the SES-CD is that its operating characteristics in terms of validation, responsiveness and reliability to assess inflammation and predict outcome in CD are still unclear.²³ Instead, empirical thresholds have been often arbitrarily proposed in the literature. The following data exemplify the currently missing consensus on the definition of endoscopic response or remission regarding SES-CD scores. The definition currently most widely accepted for endoscopic response is a reduction of $\geq 50\%$ in the baseline SES-CD score in clinical trials.²⁴ This definition has also been recommended as the first rank of endoscopic response based on SES-CD by the International Organisation for the Study of Inflammatory Bowel Disease (IOIBD).²⁵ The thresholds of current endoscopic indices for CD to define response remain unvalidated in clinical practice. In addition to the first study introducing the SES-CD score,¹⁹ there are several other published studies that use SES-CD scoring as a continuous value without applying a cut-off threshold to describe disease severity or response to therapy.^{26–28} Other studies attempted to define CD severity based on

a variety of SES-CD predefined cut-offs. In the majority of studies, inactive disease or remission was defined by a SES-CD score of 0–2^{20,29,30} or 0–3.^{31–33} Mild disease was mostly defined by a SES-CD score of 3–6,^{20,29,30,34} 4–9,^{32,33} 4–10³⁵, or as mild-to-moderate with a SES-CD score of 4–14.³¹ All these reported SES-CD cut-off values in published clinical trials were selected empirically by experts. There is no validated optimal SES-CD cut-off score and the quantification of disease severity has likewise not been standardised yet. The induction of mucosal healing, which is described as a SES-CD score of 0,^{9,36} 0–2^{20,30} or 0–3^{20,33}, is similarly inconsistent. The IOIBD presented an endoscopic remission criterion of an SES-CD of 0–2.²⁵ The randomised controlled EXTEND study, where Adalimumab efficacy was evaluated in ileocolonic patients with CD, used the SES-CD as an inclusion criterion, and defined mucosal healing as its primary endpoint.²⁷ The absence of mucosal ulcerations at week 12 was defined as mucosal healing, and was reached by 27% of adalimumab-treated patients *versus* 13% of patients in the placebo group. Further analyses identified a SES-CD score of 5.0 or below at week 12 as an optimal dichotomising point for predicting week-52 clinical remission under anti-TNF treatment in CD patients.³⁷ It remains to be further analysed, however, what degree of mucosal improvement is associated with long-term clinical benefit. Altogether, as validated cut-off values for response are missing, and as how far SES-CD score changes represent clinically meaningful outcomes has not yet been defined, adoption in clinical practice remains limited. Implementation of an endoscopic score outside of academic studies has therefore been uncommon in clinical practice, as recently shown in a large French nationwide survey.³⁸

Although a universal definition of mucosal healing is yet to be determined, the absence of ulceration at ileocolonoscopy has currently been adopted as the endoscopic endpoint for CD.⁷ Nevertheless, analyses of the SONIC trial demonstrated that partial mucosal healing, depicted as a reduction in SES-CD from baseline of >50%, may also suffice to improve clinical outcomes.³⁹ In that analysis, SES-CD reduction of >50% from baseline at week 26 of treatment was more predictive of steroid-free remission at week 52 than any of the other endoscopic cut-off values examined. Additionally, steroid-free remission at week 52 could be predicted with a sensitivity of

74% and specificity of 48%.³⁹ Further trials are urgently needed to develop an entirely new endoscopic scoring tool in CD that is objective, validated and easily applicable.⁴⁰

In addition, endoscopic assessment of postoperative recurrence of CD is also an indispensable part of optimised management of patients with CD. In a pioneering study conducted in 1990, the extent of ulcerations in the neoterminal ileum proximal to the anastomosis 1 year after ileal resection was identified as a predictor of clinical recurrence. A five-grade stepwise numeric ulcers index gradation was applied. Here, postoperative symptom recurrence could be found in 6% of patients with five or fewer aphthous ulcers in the distal ileum (Rutgeerts score i0–1), 27% in patients with more than five aphthous ulcers in the distal ileum (i2), 63% in those with diffuse ileal ulceration (i3), and 100% in examined patients with diffuse ileal ulceration with nodules or luminal narrowing (i4).⁴¹ The interobserver agreement for the Rutgeert's score was, however, rather fair, with Kappa statistics of 0.57 (95% confidence interval 0.51–0.65) in a group of 14 expert gastroenterologists in a real-life setting.⁴² The recommendation of the IOIBD expert consensus panel was to define post-operative remission as a Rutgeerts' score of ≤i1.⁷ Here, it was also proposed that the currently used i2 grade should be subdivided into i2a (purely anastomotic lesions) and i2b (lesions in the neoterminal ileum with more than five aphthous ulcers) grade, where only i2b would be judged as relevant mucosal recurrence. Again, the score lacks formal validation, and it is unclear which level of ileal inflammation constitutes clinically meaningful recurrence.

Timing of endoscopic disease assessment

The treat-to-target approach currently applied in the management of patients with CD incorporates clinical and endoscopic evaluation of disease under ongoing therapy. It is therefore of pivotal importance to objectively assess endoscopic resolution of intestinal inflammation at appropriate time points. It has been proposed that ileocolonoscopy should be performed 6–9 months after initiating a novel therapy.⁷ The assessment of postoperative anastomotic disease activity should be performed 6–12 months after intestinal resection according to the IOIBD recommendations. In patients with a high risk of recurrence (previous surgery, smokers), a more

rigid postoperative interval for the assessment of the anastomosis should be chosen.

Noninvasive biomarkers to assess mucosal healing

The mucosal inflammatory reaction in IBD is accompanied by an acute phase response detectable in the serum of the affected patients.⁴³ The only blood marker used routinely in the clinic is C-reactive protein (CRP), which has a relative short half-life of approximately 19h.⁴³ Although CRP normalisation is associated with therapeutic response, it could be shown that CRP levels correlate only modestly with endoscopic disease activity.^{7,44–46} As many as 25% of patients with demonstrable endoscopic activity did not express heightened levels of CRP.⁴⁷ This is especially the case in ileal disease. Altogether, CRP-levels can therefore not be recommended for evaluation of mucosal healing in clinical practice. Faecal calprotectin (fC) represents an attractive biomarker found in the stool of patients with CD, as it has the advantage of increased specificity for inflammatory processes of the gut. It is released by neutrophils during their activation or death, and is found to be quite stable in the faeces. However, it does not represent an IBD-specific faecal biomarker and is also elevated during other inflammatory or infectious processes. There is also remarkable intraindividual variability that must be considered, single measurements of a patient have therefore to be regarded in the longitudinal context of measurements. Regarding mucosal healing, a threshold fC level of 272 µg/g was found in a rapid test to indicate endoscopic remission (CDEIS <3), with an area under the curve of 0.933. Similar levels were found in a conventional enzyme-linked immunosorbent assay (ELISA)-based test system. The fC levels correlated best with colonic (Pearson's correlation $r=0.73$) or ileocolonic disease ($r=0.88$), but to a marked lesser extent in ileal disease ($r=0.44$).⁴⁸ Another very elegant study showed that fC measurements were able to differentiate patients with inactive (mean 104 ± 138) from mild (231 ± 244 µg/g, $p < 0.001$) activity. Here, a threshold of ≥ 70 µg/g fC demonstrated an accuracy of 87% for the detection of endoscopically active inflammation.³²

A recently conducted randomised controlled trial also evaluated the therapeutic strategy of escalating therapy by tight control based upon failure criteria defined by CRP, fC, Crohn's Disease Activity

Index (CDAI) and prednisone use (TC group) compared with clinical management relying on CDAI and prednisone use (CM group). The trial was conducted in patients with CD with endoscopic active disease that were naïve to immunomodulator or biological treatment. The primary end-point mucosal healing at week 48 was met by 46% (48/122) in the TC *versus* 30% (37/122) in the CM group ($p=0.010$). These results might have an impact on future therapeutic algorithms in CD that might include biomarker-based therapeutic decisions, and underscore the ability of CRP and fC elevation to reflect active disease in CD.⁴⁹ Further studies are warranted.

Monitoring of small bowel inflammation

Apart from assessment of inflammatory changes with standard ileocolonoscopy within the terminal ileum and the colon, monitoring of ileal lesions *via* small intestinal endoscopy has also been reported to be an effective diagnostic parameter for improved long-term outcome in patients with CD. For instance, one study retrospectively analysed 54 patients with ileal ulcers under infliximab induction and maintenance therapy.⁵⁰ Here, the proportion of patients with ileal mucosal healing (as defined by the absence of ulcers or presence of only ulcerative scars) achieving clinical remission was higher as compared with those without ileal mucosal healing (79.1% *versus* 50%, $p=0.046$). Further, the rate of long-term (>1 year) clinical remission was higher in patients with complete, i.e. ileal and colonic, mucosal healing ($p=0.025$), and the rate of major abdominal surgery was lower ($p = 0.044$) than in patients without complete mucosal healing in the ileum, suggesting the paramount importance of evaluation of ileal lesions in the monitoring of patients with CD. In a recent review,⁵¹ the potential indications for small intestinal endoscopy have been described as symptomatic patients without the possibility of assessing disease activity via other imaging techniques, or patients with persistent small-bowel lesions for excluding potential malignancies. The importance of small intestinal endoscopy, especially balloon-assisted enteroscopy (BAE), in diagnosing and evaluating pathological conditions in CD, as well as in the management of strictures ≤ 5 cm is also represented in the Japanese clinical practice guidelines for enteroscopy.⁵²

Biomarkers and noninvasive imaging techniques have, however, also been reported to be equally

effective in the evaluation of inflammation in the small intestine as compared with BAE. One prospective study of 123 patients with CD showed that the level of fC correlated with the SES-CD in patients with solely ileal disease activity ($r=0.69$, $p=0.005$).⁵³ Additionally, fC levels correlated with computer tomography enterography for the assessment of the inflammatory level of lesions and areas beyond strictures that could not be passed by BAE ($r=0.4$, $p=0.0011$). Takenaka and colleagues demonstrated in 139 patients with CD, that magnetic resonance enterography (MRE) is a reliable noninvasive imaging technique for identification of small bowel inflammation.⁵⁴ In the latter study, MRE showed high sensitivity, specificity and accuracy for the prediction of endoscopic healing on BAE (93.4%, 81.4% and 90.9%, respectively) and the kappa coefficient between BAE and MRE was substantial with $\kappa=0.73$. Moreover, BAE and MRE showed no significant difference in terms of the area under the curve for predicting clinical relapse ($p=0.26$), hospitalisation ($p=0.96$) and surgery ($p=0.89$).

MRE and ultrasonography for monitoring mucosal inflammation

While endoscopy has proven to be a sensitive method for the visualisation and evaluation of mucosal inflammation, it is limited to assessing deeper layers of the bowel. Due to the transmural inflammatory properties of CD, imaging going beyond endoluminal assessment of disease is therefore of growing importance for the exact assessment of inflammation and detection of potential complications, e.g. fistulae or abscesses.⁵⁵ MRE is the most applicable method to complement endoscopy. The detection of disease activity and severity by MRE has been reported in several studies to be higher than 80%.^{56,57} Of the MRI scores developed so far, the Magnetic Resonance Index of Activity (MaRIA), which scores wall thickness, relative contrast enhancement, mural oedema and ulcers in different segments of the GI tract, is the most widely used.⁵⁸ This score showed a highly convincing sensitivity and specificity of 0.81 and 0.89 for detecting active disease. Additionally, there was a very good per-segment correlation with the CDEIS ($r=0.82$, $p<0.001$). In a prospective study with 48 patients with CD, the MaRIA score did not significantly differ from CDEIS scores ($p=0.42$) and was moderately correlated with the degree of endoscopic change ($r=0.51$, $p<0.001$).⁵⁶ Altogether, resolution of lesions in cross-sectional imaging cannot yet

be regarded as a target of CD therapy, but MRE offers an important complementary method to assess possible transmural healing.

Ultrasound represents another important noninvasive method to assess mucosal inflammation in patients with CD. Like MRE, it avoids exposure to radiation and is furthermore available at bedside and associated with low cost. An elegant multicentre study conducted recently found that ultrasonographic examination can be used to monitor disease activity in patients with active CD. Response to therapy was associated with statistically significant reductions in bowel wall thickening or stratification, decreased fibrofatty proliferation, and increased signals in colour Doppler ultrasound.⁵⁹ The ultrasonographic subfield of multispectral optoacoustic tomography (MSOT) was tested recently for the first time in 108 patients with CD to evaluate intestinal inflammation noninvasively. MSOT allows precise localisation of specific molecules in tissues through a photoacoustic effect. This effect describes the observation that light absorbed by molecules induces thermoplastic expansion, which can be detected as ultrasound waves with very high spatial resolution. By subsequently exciting a tissue with several wavelengths, spectral unmixing techniques can be used to calculate the relative contribution of specific molecules to the overall signal with MSOT. In this way, and based on their characteristic absorption, oxygenated and deoxygenated haemoglobin have been shown to be easily detectable by MSOT. Performing noninvasive transabdominal MSOT in patients with active CD as well as those in remission demonstrated that MSOT-based assessment of total haemoglobin within the intestinal wall had an excellent correlation with the endoscopic degree of inflammation assessed by SES-CD. These preliminary data suggest that MSOT-based assessment of haemoglobin levels in the intestinal wall might have the potential to assess mucosal healing in CD patients.⁶⁰

Therapies that can induce mucosal healing in CD

Exclusive enteral nutrition

Exclusive enteral nutrition (EEN) is defined as the use of a complete liquid diet without normal dietary components for a certain time period as a sole therapeutic in patients with CD.⁶¹ This steroid-sparing method represent the first-line therapy in paediatric CD, with remission rates of 60–80%.⁶²

EEN was introduced in the 1970s and has been the treatment of choice to induce mucosal healing in paediatric patients since 1990.⁶³ However, other than in Japan, it is rarely used in adult patients and is not recommended as first-line therapy.⁶⁴ Nevertheless, several studies have investigated the efficacy of EEN for inducing clinical remission, finding remission rates varying from 20 to 100%.⁶⁵ Adherence to EEN was seen as the main obstacle to successful treatment, as up to 41% of patients were noncompliant to the initiated therapy. Recently, a pilot study with 38 adult patients (age range 16–40 years) investigated the effects on disease-related symptoms of a 2-week EEN followed by either 6 weeks of EEN or partial enteral nutrition (PEN).⁶⁶ It was found that, after 2 weeks of EEN, disease symptoms, serum CRP and FC each improved significantly, with $p=0.003$, $p=0.005$ and $p=0.028$, respectively. In the following 6 weeks therapy, improvements in symptoms were sustained in both the EEN and the PEN groups.

Corticosteroids

Corticosteroids have only limited-to-no capacity to induce mucosal healing in patients with CD. In a published study from the 1990s, the authors indicate that corticosteroids were able to induce only 12% complete mucosal healing after 4–7 weeks of steroid therapy.⁶⁷ None of the currently used endoscopic scores were used for assessment. Another study indicated no induction of mucosal healing upon corticosteroid therapy in eight patients with CD with post-operative recurrence.⁶⁸

Methotrexate

The therapeutic efficacy of methotrexate (MTX) to induce mucosal healing in patients with active CD seems limited, although available evidence is based on only a few studies. In a prospective comparative trial with azathioprine and infliximab, MTX was able to induce mucosal healing in 2/18 patients on MTX, while 9/18 on azathioprine ($p=0.011$ in comparison with MTX) and 9/15 on infliximab ($p=0.008$ in comparison with MTX) reached mucosal healing after at least 3 months of therapy.⁶⁹

Azathioprine

Azathioprine has proven able to induce mucosal healing to a certain extent in patients with CD in different studies and reports. The largest randomised

study to document the efficacy of azathioprine in this regard is the SONIC trial, which compared the efficacy of azathioprine and infliximab as respective monotherapy and combination therapy in patients with CD. Here, only 17% (18/109) of azathioprine-treated patients achieved mucosal healing at week 26.⁸

Anti-TNF antibodies

The anti-TNF antibody infliximab was the first approved biologic in 1998 for the treatment of moderate-to-severe CD.⁷⁰ In the ACCENT 1 trial, mucosal healing (absence of ulcers) was investigated in a subgroup of 99 patients with CD at week 10. Infliximab (5 mg/kg at weeks 0, 2 and 6) was able to induce mucosal healing in 29% of treated patients, compared with 3% of patients who received only one infliximab application at baseline. Subsequent maintenance therapy with infliximab (every 8 weeks) led to mucosal healing in 44% of treated patients at week 54.⁷¹ In the SONIC trial, mucosal healing at week 26 was found in 28/93 (30%) of infliximab-treated patients, compared with 18/109 (17%) of patients on azathioprine monotherapy and 47/107 (44%) of patients on azathioprine plus infliximab combination therapy.⁸ The anti-TNF antibody adalimumab proved its efficacy to induce mucosal healing in the EXTEND study of 135 patients with CD, which used complete mucosal healing (absence of ulcers) as the primary endpoint. Here, 27% of adalimumab-treated patients achieved mucosal healing at week 12 in comparison to 13% receiving placebo. At week 52, rates of mucosal healing were 24% and 0%, respectively.⁷² The property of Certolizumab pegol to induce mucosal healing was tested in the MUSIC trial, which included 89 patients with CD with endoscopic severe disease (ulceration in more than two intestinal segments and a CDEIS ≥ 8 points). At week 10 (and week 54), Certolizumab pegol was able to achieve in 37% (27%) of patients endoscopic remission (CDEIS < 5), in 10% (14%) complete endoscopic remission (CDEIS < 2) and in 4% (8%) complete mucosal healing (CDEIS = 0).⁷³ Since then, several studies on these anti-TNF-inhibitors have been performed, confirming their ability to induce and maintain mucosal healing.

Vedolizumab

Currently, there are only limited published data regarding the ability of the anti- $\alpha 4\beta 7$ integrin

antibody vedolizumab to induce mucosal healing in patients with CD. In the open-label extension phase in one tertiary centre of the GEMINI approval trial, 7/24 (29%) of patients treated for ≥ 1 year with vedolizumab exhibited mucosal healing (disappearance of ulcers⁷⁴). A recently published systematic meta-analysis of real-world effectiveness data documented that 6–63% of patients with CD treated with vedolizumab had mucosal healing at month 12.⁷⁵ The first results of prospective studies to evaluate the endoscopic response to vedolizumab therapy, similarly document its capacity to induce mucosal healing in CD.

Ustekinumab

Ustekinumab is a monoclonal antibody targeting the common p40 subunit of the IL-12 and IL-23 cytokines and is approved for the treatment of moderate-to-severe CD. The only endoscopic outcome data for ustekinumab originate from a substudy of the UNITI trials. In a *post hoc* analysis of the IM-UNITI study, mucosal healing (SES-CD score ≤ 2) was observed in 12.8%, 21.6% and 9.8% of patients who had received ustekinumab 90 mg every 12 weeks, 90 mg every 8 weeks, or placebo, respectively (nonsignificant⁷⁶).

Conclusion

The most sought-after treatment endpoint in CD has clearly shifted to resolution of intestinal inflammation. Endoscopic assessment with objective evaluation of mucosal healing has become an indispensable part in this treat-to-target approach, although we still lack a validated, easily applicable and generally acceptable definition of it. There are strong data indicating a positive correlation between objective mucosal healing and reduction in corticosteroid use, flares, hospitalisation and surgery. Furthermore, evidence is emerging that treating to an objective measure of disease activity is associated with beneficial outcomes for the individual patient with CD, although more studies must follow. Clear definitions of the level of endoscopic remission needed to achieve beneficial long-term outcomes must be defined and validated. Noninvasive biomarkers, like fC, have their limitations, but nevertheless represent valuable tools for longitudinal disease activity monitoring of the patient. Advances in endoscopic instruments and novel technological developments like MSOT might help us to better assess the level of mucosal inflammation in the future. Only precise

assessment of the level of mucosal inflammation will enable optimised therapy in CD.


Funding

CRC1811 Project C02 (RA) and DFG-SFB/TRR241 Project No. C02 (CB, RA) are funded by the German Research Council (DFG). The DFG funds the Heisenberg Professorship of RA.

Conflict of interest statement

EK reports personal fees from Pentax Europe GmbH. RA reports grants or personal fees from AbbVie, Biogen, Boehringer Ingelheim GmbH & Co. KG, DrFalk Pharma GmbH, Ferring GmbH, GlaxoSmithKline plc, InDex Pharmaceuticals AG, Janssen-Cilag GmbH, MSD Sharp & Dome GmbH, Philogen, Pfizer Inc., Roche Pharma, Stelic Institute, Sterna Biologicals, Takeda Pharma GmbH & Co. KG, Tillotts Pharma AG. MFN reports personal fees from MSD Sharp & Dohme GmbH, PPM Services S.A., Index Pharmaceuticals AB, Shire GmbH, Boehringer Ingelheim GmbH & Co. KG, Janssen Cilag GmbH, Pentax Europe GmbH, Tillotts Pharma AG, e.Bavarian Health GmbH, Takeda Pharma GmbH & Co. KG, and grants from German Research Council, German Cancer Aid, outside the submitted work.

ORCID iD

Raja Atreya  <https://orcid.org/0000-0002-8556-8433>

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