Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: November 30, 2023

Citation: Kyriacou M, Vuyyuru SK, et al., 2023. Evolution of Treatment Targets in Inflammatory Bowel Disease, Medical Research Archives, [online] 11(11). https://doi.org/10.18103/mra.v11i11.4662

DOI
https://doi.org/10.18103/mra.v11i11.4662

ISSN: 2375-1924

RESEARCH ARTICLE

Evolution of Treatment Targets in Inflammatory Bowel Disease

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ABSTRACT:
Inflammatory Bowel Disease (IBD), which encompasses Crohn's disease and ulcerative colitis, represents a chronic and progressive condition characterised by periods of active inflammation interspersed with periods of remission. The resulting disease burden, arising from patient symptoms and complications, leads to a diminished quality of life for individuals with IBD. Despite significant advancements in the management of IBD, the ideal treatment targets are uncertain. The evolution of treatment targets in IBD signifies a paradigm shift from mere symptom control to a more holistic approach that aims at achieving deeper remission and improving patients' quality of life. The "treat-to-target" paradigm, guided by international consensus and expert insights, emphasises the importance of tailoring therapeutic goals to individual patient needs and disease severity. As our understanding of IBD's underlying mechanisms deepens and therapeutic options expand, treatment goals have evolved to include not only clinical response but also the pursuit of more objective endpoints such as endoscopic healing. Emerging targets, such as the assessment of transmural healing through cross-sectional imaging and the focus on histologic remission as a predictor of long-term outcomes, hold great promise in further refining IBD management strategies. However, further research is needed to recommend these treatment targets in clinical practice. In the review we explore the ongoing evolution of treatment targets in IBD aimed at optimising patient outcomes and ultimately improving quality of life (QoL).

Introduction

Inflammatory Bowel Disease (IBD) encompasses a group of chronic inflammatory disorders (ulcerative colitis [UC] and Crohn's disease [CD]) that primarily affect the gastrointestinal (GI) tract.[1] It was estimated that approximately 6.8 million people are currently diagnosed with IBD globally which amounts to a global prevalence of up to 84.3 per 100,000 persons in 2017 with highest burden in Europe and increasing incidence in newly industrialised countries.[2,3] IBD is characterised by periods of active inflammation interspersed with periods of remission, displaying a varied range of clinical manifestations including abdominal discomfort, chronic diarrhoea, rectal bleeding and weight loss which can significantly impact a patient's quality of life (QoL).[4]

The approach to disease monitoring in IBD has undergone significant shifts over time, reflecting advances in our understanding of the disease's underlying mechanisms. Early interventions within IBD primarily revolved around corticosteroids and immunosuppressants.[5,6] The emergence of advanced therapies marked a significant turning point, with the introduction of anti-tumour necrosis factor (anti-TNF) agents, such as infliximab followed by agents targeting integrin receptors, IL-12/23 and janus kinase receptors (JAKi). Beyond symptom alleviation, these agents demonstrated the capacity to both induce and sustain mucosal healing,[7] shifting the treatment paradigm towards more targeted approaches.

Formerly, emphasis was placed on symptom control alone; however, it has become evident that symptom remission does not necessarily translate to underlying inflammation resolution or the prevention of disease progression.[8,9] Subsequently, availability of advanced tools such as endoscopy, computerised tomography (CT), magnetic resonance imaging (MRI), small bowel ultrasound (US) and biomarkers like faecal calprotectin (FCP) allowed objective monitoring of disease activity. However, these advancements have also introduced added intricacies to treatment strategies, involving decisions about drug sequencing, initiation, dosage adjustments, discontinuation, and surgical considerations.[10] Consequently, this complexity has spurred discussions on new treatment objectives and targets, encompassing histological healing, transmural healing, and molecular-based measures. Additionally, the utilisation of patient-reported outcomes (PROs) such as the two-item PRO Index (PRO2)[11] and the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)[12] acknowledges the multidimensional impact of IBD on patients' lives beyond clinical manifestations.

The concept of "treating to target" has gained prominence in recent years, directing treatment based on specific therapeutic objectives and the updated Selecting Therapeutic Targets in IBD (STRIDE-II) initiative have laid out time-dependent (short-, intermediate- and long-term) objective treatment targets which are summarised in Table 1. By setting specific therapeutic goals and adjusting treatment regimens based on objective measures of disease activity, this strategy aims to optimise patient outcomes. This review will explore the ongoing evolution of treatment targets in IBD aimed at optimising patient outcomes and ultimately improving QoL.

Evolution of Treatment Targets within IBD:

CLINICAL INDICES AND PATIENT REPORTED OUTCOMES:

Historically, the evaluation of IBD relied on subjective clinical judgment. The Crohn's Disease Activity Index (CDAI)[13] for CD and the Truelove and Witts Severity Index[14] for UC were among the first attempts to quantify disease activity. These early indices integrated symptoms such as bowel movements, physical findings, and laboratory parameters such as erythrocyte sedimentation rate (ESR) to provide a composite score, aiding in treatment decisions. However, they had limitations, such as subjectivity and a lack of consideration for endoscopic and histological findings.

However in IBD, clinical symptoms prove to be an unreliable gauge of mucosal disease activity[15] and frequently substantial mucosal inflammation is seen in those deemed to be in complete clinical remission.[16] One study on CD revealed that relying solely on clinical symptoms alone for treatment escalation resulted in a decreased rate of endoscopic healing, in comparison to employing a composite strategy that incorporated both clinical and biochemical activity assessment (including FCP and C-reactive protein [CRP]).[17] Given the weak correlation between clinical symptoms and endoscopic disease activity, there is a potential for undertreatment in CD using traditional methods of management involving stepwise escalations. This poses the risk of treatment delays in individuals at a greater risk of disease advancement.[18] Additionally, it has been found that there is a weak correlation ($r=0.38$) between the CDAI and the actual disease activity observed through endoscopic examinations.[19] One study determined that the CDAI is influenced by factors with no relation to inflammatory activity and recommends the adoption of objective measures, such as endoscopic indices, for the purpose of defining disease activity.[20]

Table 1.
Summary of treatment target and time-point recommendations based on the Selecting Therapeutic Targets in IBD II (STRIDE-II) Consensus

	Treatment targets	***Time-point***
Clinical	Clinical response	Immediate
	Clinical remission	Short- to intermediate
Endoscopic and transmural assessment	Endoscopic response	Intermediate
	Endoscopic healing	Long-term
	Transmural healing - Not a formal target, possible adjunct in CD	
	Histological remission - Not a formal target, possible adjunct in UC	
Biomarkers	Normalisation of CRP	Short- to intermediate
	Reduction of FCP	Intermediate
QoL and disability	Absence of disability and normalised health related QoL	Long-term

CD, Crohn's disease; UC, Ulcerative colitis; CRP, C-reactive protein; FCP, faecal calprotectin; QoL, Quality of life

Unlike CD, clinical symptoms in UC show a positive correlation with the extent of inflammation observed during endoscopy. Key clinical objectives in UC patients include achieving normal stool frequency and the absence of rectal bleeding. Notably, the lack of diarrhoea and blood is an autonomous predictor of outcomes, such as relapse and surgical intervention.[21] The Mayo Clinic Score (MCS) evaluates disease severity by considering stool frequency, rectal bleeding, endoscopy findings, and the physician's global assessment.[22] However, achieving clinical remission by the MCS can still allow some blood in stool. Complete clinical remission characterised by normal stool frequency and the absence of blood or abdominal pain is closely linked to endoscopic healing or nearly endoscopic healing (indicated by a Mayo Endoscopic Subscore (MES) of 0 or 1) in around 80% to 90% of patients. Therefore, clinical measures of stool frequency and rectal bleeding, subjective items of the MCS and PRO-2, have a moderate to strong correlation with endoscopic activity in UC.[23] Consequently, in the context of UC, clinical response and remission hold significant value as short-term targets, more relevance than in CD.[10]

Recognising the significance of patient perspectives, newer indices have incorporated PROs, acknowledging the divergence in viewpoints between patients and their physicians when assessing health concerns and treatment targets.[24] Frequently utilised PROs in IBD include PRO-2 which encompasses abdominal pain and stool frequency in CD and rectal bleeding and stool frequency in UC. PRO-3 expands on PRO-2 by incorporation an additional element of overall well-being.[11] Given the robust correlation between PROs and patient well-being, it becomes imperative to regularly assess this target throughout the disease trajectory. However, there's a requirement for a validated PRO that can effectively identify symptoms that both hold clinical significance and are meaningful to patients.[25]

The STRIDE-II initiative found that patients prioritise the addressment of clinical symptoms. Here, the treatment aims of clinical response and remission were ranked in the top 3 of most important short-term treatment goals across both CD and UC. Consequently, the majority of experts within the Delphi group regarded alleviating symptoms (clinical response followed by clinical remission) as significant short-term and intermediate treatment objectives. In this context, clinical response in adults is defined as a reduction of at least 50% in PRO2 (stool frequency and abdominal pain) for CD, and a reduction of at least 50% in PRO2 (stool frequency and rectal bleeding) for UC. Clinical remission is defined as PRO2 (abdominal pain ≤ 1 and stool frequency ≤ 3) or Harvey-Bradshaw index (HBI) <5 in adults in CD and PRO2 (rectal bleeding $= 0$ and stool frequency $= 0$) or partial

Mayo (<3 and no score >1) for UC. Therefore, achieving clinical response is recommended as an immediate and clinical remission as a medium-term (i.e. intermittent) treatment target, and it is essential to contemplate management modifications if these objectives are not met. STRIDE-II states clinical response or remission alone lack adequacy as long-term treatment objectives and objective improvement in measures of inflammation should be demonstrated when considering clinical remission in terms of an intermediate treatment target.[10]

ENDOSCOPIC HEALING:

The disconnection between symptoms and mucosal inflammation is particularly wide in CD and as previously mentioned, treatment escalation based on symptoms alone does not lead to higher rates of clinical remission. The current approach to managing IBD emphasises achieving early endoscopic healing, as this has the potential to avert the progression towards complications.[26] Achieving endoscopic healing was associated with fewer hospital admissions and surgery in CD and fewer colectomy rates in UC.[27,28] Endoscopic remission is therefore a fundamental long-term target as emphasised in STRIDE-II, with the additional note of endoscopic response being suitable as a short-term treatment target.[10]

Endoscopic assessment in Crohn's disease:

The initial validated assessment tool for endoscopic disease activity in CD was the Crohn's Disease Endoscopic Index of Severity (CDEIS).[29] This index involves evaluating four types of lesions (superficial ulcers, deep ulcers, ulcerated stenosis, or non-ulcerated stenosis) in five ileocolonic segments: terminal ileum, ascending colon, transverse colon, descending and sigmoid colon, and the rectum.[30] However, due to its complexity, it proved less practical for everyday clinical use. Consequently, the Simple Endoscopic Score for Crohn's Disease (SES-CD) was introduced as a more user-friendly alternative. The SES-CD evaluates the parameters of ulcerated and affected surfaces, ulcer size and stenosis, offering a more approachable way to assess endoscopic severity.[31] In the context of STRIDE-II, the evaluation of endoscopic healing can be conducted using sigmoidoscopy or colonoscopy, and in cases where these methods are not feasible, alternatives such as capsule endoscopy (CE) or balloon enteroscopy can be employed in the assessment of CD.[10] However, ileo-colonoscopy is hindered by factors such as cost, invasiveness, sedation requirements, and patient tolerance.[32] Additionally, due to its inability to be performed repeatedly, ileocolonoscopy has a restricted role in tight monitoring strategies. Furthermore, situations like proximal small bowel disease can make mucosal assessments unfeasible.[10] As approximately 80% of CD patients have small bowel involvement,[33] evaluating the small bowel through CE or balloon endoscopy is a critical aspect of IBD evaluation.[34,35]

Endoscopic assessment in ulcerative colitis:

There are currently two main scoring systems used in UC as reliable measures of endoscopic disease activity: the sigmoidoscopic component of the MES and Ulcerative Colitis Endoscopic Index of Severity (UCEIS).[36,37] The MES assesses the vascular pattern, the reliability and the presence of erosions during endoscopy and produces a score from 0 to 3. The appeal of the MES is its simplicity, however the UCEIS may be more responsive as it has a wider scoring range (0–8) taking into account the evaluation of vascular pattern, bleeding and presence of erosions/ulcerations with each being graded by level of severity.[38] Furthermore, the UCEIS has shown remarkable prognostic significance during severe UC flares. One study has highlighted that a UCEIS score of ≥7 upon admission is associated with a requirement for treatment escalation beyond steroids, often involving infliximab or ciclosporin, in a substantial proportion of patients.[39]

Despite the acknowledged significance of endoscopic findings in the "treat-to-target" approach, there is a lack of consistency regarding the most suitable definition of endoscopic response and remission. Accordingly, for CD, STRIDE-II has adopted the following definitions based on expert consensus: an endoscopic response entails a reduction of more than 50% in the SES-CD or CDEIS. For endoscopic remission, it involves a SES-CD score of 2 points or lower, or a CDEIS score below 3, combined with the absence of ulcerations, including aphthous ulcers.[10] In UC, endoscopic healing is often defined as a MES of ≤1. However, research indicates that achieving a MES of 0 is linked to better disease outcomes, including a reduced likelihood of clinical relapse and colectomy.[40,41] As a result, the term "endoscopic improvement" has been used to describe a MES of 1, rather than considering it as true remission.[26] Additionally, differing viewpoints have emerged regarding whether a UCEIS of 0 or 1 is more appropriate to define endoscopic remission, with the STRIDE-II guidelines proposing a cut-off value of 1.[10]

SERUM AND FAECAL INFLAMMATORY BIOMARKERS:

Although endoscopy offers direct assessment of the intestinal mucosa, non-invasive and cost-effective biomarkers such as CRP and the more recent FCP have grown in significance for evaluating disease

activity and treatment response in IBD.[42] This transition is highlighted in the STRIDE-II guidelines, as after attaining clinical remission, the most relevant intermediate target involves achieving normalisation of CRP levels (to values under the upper limit of normal) and reducing FCP levels to the range of 100–250 µg/g.[10] This adjustment represents a departure from the previous STRIDE-I approach, which only considered biomarkers as supplementary measures.[43] Additionally, although endoscopy is the gold-standard for confirming mucosal healing biomarkers provide the advantage of easy repetition and are routinely used in clinical practice.[44] By adjusting drug therapy based on biomarker targets, clinicians can enhance disease control, offering a more effective approach compared to relying solely on endoscopy or symptomatic indicators alone.[42]

The CALM study marked a significant milestone by being the first randomised controlled phase study to provide strong evidence supporting the effectiveness of treating to a biomarker end point in IBD management. The study involved the participation of patients with active endoscopic CD who were randomised to either a tight control group, where treatment escalation decisions were guided by specific biomarker thresholds, or a clinical management group where treatment was escalated based solely on clinical criteria. The tight control group's treatment was adjusted based on factors such as FCP levels exceeding 250 µg/g, CRP levels surpassing 5 mg/L, CDAI reaching 150, or prednisone use in the previous week. The tight control group demonstrated higher rates of endoscopic remission at the 1-year mark. The primary outcome was mucosal healing defined as a CDEIS score below 4 with the absence of deep ulcers after 48 weeks and post hoc analysis of the study demonstrated that a CRP <5 mg/dL in combination with FCP <250 µg/g was the best predictor of achieving this primary outcome.[17,45] Additionally, another study that analysed long-term data from the CALM trial discovered that patients diagnosed with CD, who achieve either endoscopic or deep remission following one year of intensive treatment, experience a reduced likelihood of disease progression with a lower risk of major adverse events (internal or perianal fistula/abscess, stricture, hospitalisation, or surgery).[46]

C-REACTIVE PROTEIN:

C-reactive protein is commonly utilised as a serum biomarker to predict clinical activity in inflammatory conditions, including IBD and its short half-life enables a rapid CRP response that aligns with the levels of inflammation.[47] Nevertheless, its specificity is limited due to its elevation in systemic inflammatory diseases beyond the intestinal tract and additionally, significant variability exists in the CRP response between CD and UC.[48,49] In terms of its correlation with endoscopic disease activity, CRP demonstrates a high specificity (pooled specificity 0.92, 95% CI 0.72–0.96) but low sensitivity (pooled sensitivity 0.49, 95% CI 0.34–0.64) and therefore, low CRP levels do not necessarily indicate the absence of such activity.[50]

In the case of CD, the occurrence of active lesions is strongly indicated by a positive CRP result due to its high specificity.[51] One study discovered that 92.9% of CD patients with clinical symptoms exhibited normal CRP levels in laboratory data, despite the majority of their detected lesions showing mild inflammation. This suggests the potential to exclude severe endoscopic lesions in clinically active CD patients with a negative CRP result.[52] In CD, maintaining low levels of CRP has been correlated with a decreased likelihood of experiencing clinical relapse.[53-55] A post-hoc analysis from ACCENT-I highlighted CRP as an indicator for sustained response or remission to infliximab, demonstrating CRPs ability to predict treatment response.[56] Additionally, one study associated high CRP levels in CD patients with non-response to infliximab treatment.[57] The data strongly indicates that achieving a decreased or low CRP value following treatment is associated with a more positive prognosis in IBD. However, there remains debate over whether baseline CRP levels can reliably predict treatment response.[58]

While CD is linked to a robust CRP response, UC exhibits only a moderate to negligible CRP response and a proposed theory for this distinction is that inflammation in UC is limited to the mucosa, as opposed to being transmural in CD.[49] One study investigated the relationship between CRP levels and endoscopic severity indices in 552 UC patients undergoing 722 endoscopies. Comparing these indices with CRP levels, the study found moderate correlations, with Pearson's correlation coefficients ranging from 0.457 to 0.523. However, CRP alone demonstrated limited sensitivity (50.5-53.3%) and specificity (68.7-71.3%) for detecting endoscopic remission across the five indices. The findings indicate that while CRP levels moderately correlate with endoscopic activity indices in UC, they are insufficient to accurately reflect endoscopic severity, especially for detecting remission.[59]

Additionally, it has been found that around 15% of healthy individuals have an absent CRP response and therefore this biomarker should not be relied on as a sole assessment of disease activity in IBD.[50]

STRDE-II current recommendation is that achievement of a normal CRP level, defined as a value below the upper limit of normal or <5 mg/dL, following treatment initiation should be acknowledged as a mandatory treatment goal in the short- or intermediate-term but it is, at present, inadequate as a long-term target.[10]

Faecal calprotectin:

It's well established that the concentration of FCP detected in faeces corresponds to the extent of neutrophil influx, into the bowel lumen, from the inflamed intestinal wall.[60,61] Therefore, FCP stands as a dependable biomarker for intestinal inflammation and is commonly utilised as a sensitive non-invasive indicator of disease activity in IBD.[62] It has been demonstrated that FCP exhibits higher sensitivity than CRP for detecting endoscopic inflammation, albeit with lower specificity, in IBD. A large meta-analysis reported the pooled sensitivity and specificity estimates for CRP were 0.49 and 0.92 and for FCP were 0.88 and 0.73, respectively.[50]

A novel study from 1997 was one of the first to establish a notable link between FCP levels and endoscopic, as well as histologic activities, among UC patients.[63] Since then many studies have shown a strong correlation between FCP levels and endoscopic activity in IBD. One study, conducted on 77 patients with CD, indicated that a FCP cut-off of 200 µg/g could anticipate endoscopic activity with a sensitivity of 70% and specificity of 92%.[64] A separate study highlighted a stronger correlation between FCP and disease endoscopic activity in UC when compared to the Rachmilewitz clinical activity index. Furthermore, this study reported an overall accuracy of 89% for FCP in identifying endoscopically active disease.[65] Additionally, another investigation highlighted that individuals with IBD who were clinically in remission and displayed FCP levels below 50 µg/g exhibited normal colonoscopy outcomes.[66] These intriguing observations suggest that FCP holds potential as a biomarker for assessing endoscopic activity and mucosal healing in individuals with IBD. A recent meta-analysis from 2023, involving 24 prospective studies, aimed to assess FCP's effectiveness in predicting IBD relapse. Here, the pooled sensitivity and specificity of FCP were 0.720 and 0.740, respectively. The findings suggest that FCP is a valuable, cost-effective biomarker for early IBD relapse prediction, with an FCP value of 152 µg/g being an effective threshold for identifying patients at higher relapse risk.[67]

Despite the apparent strong correlation between endoscopic activity and FCP levels observed, some more recent studies have presented a relatively weaker correlation. In one study using the MES to assess endoscopic activity in UC, FCP at a threshold of 170 µg/g demonstrated a sensitivity of 69% and a specificity of 65% for distinguishing active endoscopic disease (MES 2 or 3) from inactive disease (MES 0 or 1).[68] In a different study, FCP at a threshold of 250 µg/g showed a sensitivity of 67% and specificity of 77% for distinguishing MES ≤ 1 in patients with UC.[69] A commonly agreed upon and extensively researched threshold for indicating active inflammation in both UC and CD is 250 µg/g.[70] However, due to its low reliability, there is a range of uncertainty in interpreting FCP values and it's worth noting that even values below 600 µg/g can still be indicative of minimal inflammation. Regarding endoscopic healing, STRIDE-II supports an FCP cut-off value of 150 µg/g. Additionally, a more stringent threshold of 100 µg/g is suggested as an indicator of deep healing, encompassing both endoscopic and transmural healing. Therefore, reducing FCP to the levels of 100–250 µg/g have been suggested as intermediate treatment targets by STRIDE-II.[10]

CROSS SECTIONAL ASSESSMENT:

Uncontrolled progression of inflammation in CD can give rise to complications like strictures, fistulas and abscesses, which occur in around 20-30% of patients upon diagnosis. The transmural inflammation of the bowel wall can lead to the formation of sinus tracts, which can progress to fistula formation, an unfavourable outcome.[71] Although mucosal healing is currently acknowledged as a prominent treatment target in CD, it's important to note that even among patients who achieve sustained mucosal healing, there can still be residual inflammation within the bowel wall that is detectable through cross-sectional imaging techniques.[72] In a study involving paediatric patients with CD, it was observed that approximately one in every four patients exhibiting mucosal healing still displayed features of transmural inflammation.[73] Consequently cross-sectional imaging have become essential for the assessment of transmural inflammation in patients with IBD, addressing some of the limitations encountered with endoscopy, and with its ability in diagnosis, staging and assessment of disease severity.

Magnetic resonance imaging stands out as the most widely utilised and established imaging technique for CD and can be used for accurate therapeutic monitoring in colonic CD.[74] Additional cross-sectional imaging modalities used include magnetic resonance enterography (MRE), contrast-enhanced CT and US.[10] Studies have indicated the high

diagnostic accuracy of both MRI and CT in detecting small bowel CD. However, it emphasises that CT involves ionising radiation exposure, making MRI a radiation-free option with the potential to serve as the primary imaging modality for small bowel CD.[75] To standardise MRE assessment in CD, scoring systems like the Magnetic Resonance Index of Activity (MaRIA) and its simplified version (MaRIAs) have been developed. They are both recognised for quantifying transmural inflammation in CD, applied to the terminal ileum and colon and correlating well with the CDEIS.[26,76,77] One study found that achieving radiological response, assessed by CTE or MRE, is linked to improved long-term outcomes (e.g. lower risk of hospitalisation/surgery) and could serve as a potential treatment goal for individuals with small bowel CD.[78] Nevertheless, there is a lack of established criteria for precisely quantifying transmural healing in cross-sectional imaging, underscoring the need for prospective studies in this area.[79] Additionally, MRI has several drawbacks, including the need for timely access to imaging facilities, cost considerations, and the expertise of specialist radiologists for interpretation.[74] Additionally, many of the scoring systems associated with MRI can be labour-intensive to execute, thereby limiting its suitability as a routine monitoring tool and rendering them impractical for everyday clinical use. STRIDE-II suggests using the MaRIA score to help define resolution of inflammation on MRI, used as an adjunct assessment in IBD monitoring.[10,80]

Role of bowel ultrasound in assessing transmural inflammation:

The incorporation of bedside bowel US has transformed our capacity to evaluate the extent of inflammation in IBD. It offers the benefit of surveying the entire GI tract and permits frequent evaluation that is well tolerated by patients.[10,81] Additionally, studies have shown that US can effectively monitor disease activity and transmural changes in response to medical treatment for active CD.[82] The METRIC trial investigated the diagnostic accuracy of MRE and small bowel US for determining the extent and activity of newly diagnosed and relapsed CD. The study found that MRE had a sensitivity of 97% and US had a sensitivity of 92% for detecting small bowel disease. The specificity was 96% for MRE and 84% for US. It concluded that both MRE and US are highly sensitive in detecting small bowel disease and are considered valid initial assessments, potentially replacing ileocolonoscopy. However, in a National Health Service (NHS) context, MRE is typically preferred due to its superior sensitivity and specificity compared to US.[83] Furthermore, a recent survey revealed that there is a considerable proportion of healthcare centres in the United Kingdom which lack adequate access to US services for the assessment of CD.[84]

Transmural healing:

Transmural healing encompasses the restoration of all layers of the intestinal wall, acknowledging that inflammation in CD, and likely in UC too, extends beyond the mucosal layer. The thickening of the bowel wall and, in certain instances, a reduction in lumen diameter are characteristic effects of transmural inflammation. Proposed definitions for transmural healing frequently involve the normalisation of bowel wall thickness within the affected segments.[85] Transmural healing in CD has been linked to considerable enhancements in disease-related outcomes, however there is no universally accepted definition. A systematic review from 2021 summarised the commonly utilised definitions using the modalities of MRE, bowel sonography, and CT to assess transmural healing. Predominantly, bowel wall thickness below 3 mm emerged as the most prevalent criterion to define transmural healing. Doppler US to gauge vascularisation and the absence of complications or contrast enhancement were also utilised for this purpose.[86] One study highlighted that patients with CD who achieved transmural healing experienced more favourable long-term outcomes, including reduced hospital admissions and therapy escalation, compared to those with mucosal or no healing.[72]

Many studies have shown that transmural healing, especially in CD, may emerge as a future treatment target aimed at improving patient outcomes. However, clear and definitive criteria for accurately quantifying transmural healing through cross-sectional imaging have not been established, and the need for prospective studies in this area is evident.[79,87] Additionally, due to the current limitations of available treatments, achieving transmural healing remains challenging. Although STRIDE-II did not establish transmural healing as an official treatment target, its recognition as an adjunctive assessment has gained momentum making it an important consideration for achieving a deeper level of healing, especially in CD.[10]

HISTOLOGY:

In recent years, there has been growing interest in exploring histologic remission in IBD, driven by the notion that achieving deeper levels of remission leads to improved outcomes.[10] The pursuit of histological remission in IBD stands as an aspirational therapeutic objective that has yet to become a standard practice in clinical management. One study revealed that patients who

attained histological remission experienced more positive outcomes compared to those with ongoing histological disease activity, particularly in the context of UC. This underscores the potential benefits of targeting histological healing to optimise treatment strategies for IBD.[88]

Despite this, the precise role of histology in IBD management remains unclear. There is an ongoing need to better define and understand the implications of histological remission in the context of IBD. Furthermore, there is a current lack of validated histological scores utilised in IBD, highlighting the need for scoring systems capable of quantifying the extent of microscopic activity.[89] Another contributing factor, mentioned in STRIDE-II, is the restricted efficacy of currently available treatments in inducing histologic remission, particularly notable in the case of CD.[10] One study, investigated the efficacy and safety of infliximab and adalimumab in achieving histological remission, revealed that merely 13% of CD patients undergoing prolonged anti-TNF regimens managed to attain such remission.[90] Due to the above reasons, histological remission is not suggested as a primary treatment target in CD or UC as per the current STRIDE-II guidance. However, in the case of UC, it could serve as a supplementary measure to endoscopic remission, indicating a more comprehensive level of healing.[10]

QUALITY OF LIFE AND DISABILITY:

Patients with IBD frequently experience reduced QoL, which is manifested by elevated rates of co-morbid anxiety and depression found in comparison to healthy individuals.[91] For adults, there is compelling evidence indicating that QoL deteriorates during periods of active disease, with potentially greater impact observed in those with CD.[92] Additionally, it has been shown that decreased QoL and heightened disability are linked to higher indirect medical costs associated with IBD.[93]

The recent STRIDE-II consensus highlights the enhanced significance of health-related QoL as a pivotal endpoint in the comprehensive management of IBD. It emphasises the inclusion of QoL restoration and disability reduction as formal long-term treatment targets, independent of other objective markers of inflammation. This suggests that even if deep healing is achieved, treatments affecting QoL should be re-evaluated. Balancing different targets, including endoscopic healing, requires shared decision-making with patients. Overall, regular assessment of IBD patients should consider multiple aspects such as QoL, disability, fatigue, mental health, and body image.[10]

Conclusion:

The evolution of treatment targets in IBD signifies a paradigm shift from mere symptom control to a more holistic approach that aims at achieving deeper remission and improving patients' QoL. The "treat-to-target" paradigm, guided by international consensus and expert insights, emphasises the importance of tailoring therapeutic goals to individual patient needs and disease severity. As our understanding of IBD's underlying mechanisms deepens and therapeutic options expand, treatment goals have evolved to include not only clinical response but also the pursuit of more objective endpoints such as endoscopic healing. Emerging targets, such as the assessment of transmural healing through cross-sectional imaging and the focus on histologic remission as a predictor of long-term outcomes, hold great promise in further refining IBD management strategies. By incorporating these advanced objectives, clinicians are poised to make more informed treatment decisions including multidimensional assessments that integrate PROs, clinical and endoscopic findings. While the ultimate objective might involve achieving comprehensive deep healing (including clinical remission along with complete endoscopic, histological, and transmural healing), further investigation is necessary to assess the incremental benefits of this goal and whether it justifies the potential risks and associated treatment expenses. Furthermore, attaining this broader objective remains challenging for the majority of patients with the presently available therapies.[10] Ongoing clinical trials exploring optimal treatment targets for the management of IBD are likely going to provide definitive answers (VERDICT trial [NCT04259138], QUOTIENT [NCT05230173]). As we continue to explore these new horizons, the ultimate goal remains the enhancement of patient well-being and overall QoL, optimisation of patient outcomes and achievement of sustained, deep remission.

Conflicts of Interest Statement:

Prof Gordon William Moran (GWM) is in receipt of research funding from Jansen, Astra Zeneca and Bristol Myers Squib. Prof GWM attended advisory boards for Abbvie and Pfizer. Prof GWM is a consultant for Alimentiv and EndoRead.

All other authors (MK, SKV) have no conflicts of interest to declare.

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