Crohn's disease management: translating STRIDE-II for UK clinical practice

Karen Kemp, Mark A. Samaan, Ajay M. Verma and Alan J. Lobo

Ther Adv Gastroenterol

2024, Vol. 17: 1–16

DOI: 10.1177/17562848241280885

***Abstract*:** Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterised by endoscopic inflammation, progressive bowel damage and gastrointestinal lesions. Although treatment strategies for CD have traditionally focused on a stepwise pharmacological approach to achieve clinical remission or symptom resolution, these treatment goals correlate poorly with disease activity. Thus, achieving full clinical remission and full endoscopic healing alone may be insufficient, as patients may remain at risk of inflammatory complications. Individualised 'treat-to-target' (T2T) pharmacological and treatment approaches represent a promising strategy for improving endoscopic remission and symptom resolution among patients with CD. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) and STRIDE-II guidelines, launched in 2013 and later renewed, identified individualised targets for a T2T therapeutic approach for patients with IBD. These guidelines facilitate the individualisation of target treatment goals through evidence-based, long-term (health-related quality of life, absence of disability, endoscopic healing) and intermediate/short-term (abdominal pain, stool frequency, normalisation of biomarker levels) treatment targets, allowing patients and clinicians to consider the risk-to-benefit balance of goals and selected therapeutic strategies. This article aims to summarise the STRIDE-II guidelines and provide intellectual guidance for healthcare professionals to apply the STRIDE-II principles to current clinical practice in the United Kingdom (UK). Management recommendations for primary and secondary first-line non-responders are provided, along with suggestions for utilising the endoscopic outcomes scoring system in UK clinical practice.

Declaration of interest: This article was commissioned and funded by Takeda UK Ltd, who suggested the author and topic. Takeda UK Ltd also reviewed and approved the content. Prescribing information and adverse event reporting can be found at the end of the article.

Plain language summary

Best practice suggestions for incorporating STRIDE-II into UK clinical practice for the management of patients with Crohn's disease

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterised by endoscopic inflammation and damage, estimated to affect approximately 11 individuals per 100,000 annually in the United Kingdom (UK). Traditional treatment strategies for IBD, including CD, focus on symptom resolution and clinical remission. However, as symptom resolution correlates poorly with disease activity, a treatment goal of full clinical remission and full endoscopic healing alone may be insufficient. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) and STRIDE-II initiative released 'treat-to-target' therapy evidence-based guidelines, detailing individualised clinical treatment targets for patients with IBD. STRIDE-II accommodates treatment individualisation through several long-term (health-related quality of life, absence of disability, endoscopic healing) and intermediate/short-term (abdominal pain, stool frequency, normalisation of biomarker levels) treatment targets, allowing patients and clinicians to consider the risk-to-benefit balance of goals and selected therapeutic strategies. This article provides best practice

Correspondence to:
Karen Kemp
Department of Gastroenterology, Manchester Clinical Academic Centre, Manchester Royal Infirmary, University of Manchester, Oxford Road, Manchester M13 9WL, UK
karen.kemp@mft.nhs.uk

Mark A. Samaan
Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

Ajay M. Verma
Kettering General Hospital NHS Foundation Trust, Kettering, UK

Alan J. Lobo
Inflammatory Bowel Disease Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Broomhill, Sheffield, UK

suggestions for healthcare professionals to apply the STRIDE-II principles to current clinical practice in the UK. Management recommendations for primary and secondary first-line non-responders are provided, along with suggestions for utilising the endoscopic outcomes scoring system in UK clinical practice.

Keywords: best practice, Crohn's disease, guidelines, inflammatory bowel disease, STRIDE-II, UK clinical practice

Received: 4 April 2024; revised manuscript accepted: 19 August 2024.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterised by gastrointestinal lesions, mucosal or endoscopic inflammation and progressive bowel damage.[1,2] The annual incidence of CD is estimated to be approximately 11 individuals per 100,000 in the United Kingdom.[3] Treatment strategies for CD in clinical practice have traditionally focused on symptom control, often via a stepwise pharmacologic therapeutic approach which may include surgical resection in refractory patients.[4–6] However, symptom resolution and CD activity are poorly correlated, suggesting that patients who achieve symptom resolution may remain at risk of inflammatory complications.[7] By contrast, the widely adopted 'treat-to-target' (T2T) approach has the potential to improve endoscopic and clinical outcomes through individualised goal-directed treatment strategies.[8,9] Understanding targets for individual treatment options is thus crucial for utilising T2T strategies in UK clinical practice.

In 2013, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative was launched by the International Organization for the Study of IBD (IOIBD) to identify treatment targets and goals for IBD. The STRIDE-I (2015)[10] and updated STRIDE-II (2021)[11] guidelines provide evidence-based recommendations for short- and long-term therapeutic targets, focusing on the T2T management of IBD in clinical practice. The key framework of the STRIDE-II guidelines facilitates target individualisation and adaptation to local resources to improve IBD-associated clinical outcomes.[11] This article aims to summarise the STRIDE-II guidelines and provide guidance to healthcare professionals (HCPs) on how best to apply the principles of STRIDE-II to current clinical practice in the United Kingdom. Although STRIDE-II includes guidance for both adults and children with IBD (CD or ulcerative colitis (UC)), this article focuses exclusively on adults with CD.

T2T and CD treatment goals in UK clinical practice

T2T is a collaborative approach between the patient and clinician, which focuses on achieving pre-specified treatment targets that correlate with the risk of disease progression.[1,8] The identified target guides the selection of first-line treatment and is periodically re-assessed throughout the disease course to allow for treatment adjustments or adaptations as needed (Figure 1).[11] This approach enables the individualisation of care and appropriate early treatment choices, which is associated with improved long-term clinical outcomes in patients with CD.[12] Importantly, T2T also allows for therapy adjustments according to fluctuating disease severity and risk-to-benefit ratios.[11]

Previous clinical trials have demonstrated that T2T approaches that target endoscopic lesions and biomarker levels and aim to lower the risk of endoscopic recurrence significantly improve medium-term clinical and endoscopic outcomes in patients with CD.[13–15] The STRIDE-II guideline recommends key T2T objectives, including endoscopic healing and normalisation of inflammatory biomarker levels, which support sustained clinical remission.[11] Given the importance of minimising early disease activity to improve prognosis, T2T may be a favourable management approach for patients with IBD, including those with CD.[9]

Short-, intermediate- and long-term treatment targets for patients with CD

The 2015 STRIDE guidelines proposed important targets for T2T management of adults with CD, including clinical or patient-reported remission of abdominal pain, diarrhoea/altered bowel habits and endoscopic remission. Normalisation of the levels of key inflammatory biomarkers – C-reactive protein (CRP) and faecal calprotectin (FC) – was considered an adjunctive target for monitoring endoscopic healing.[10] In 2021, STRIDE-II was

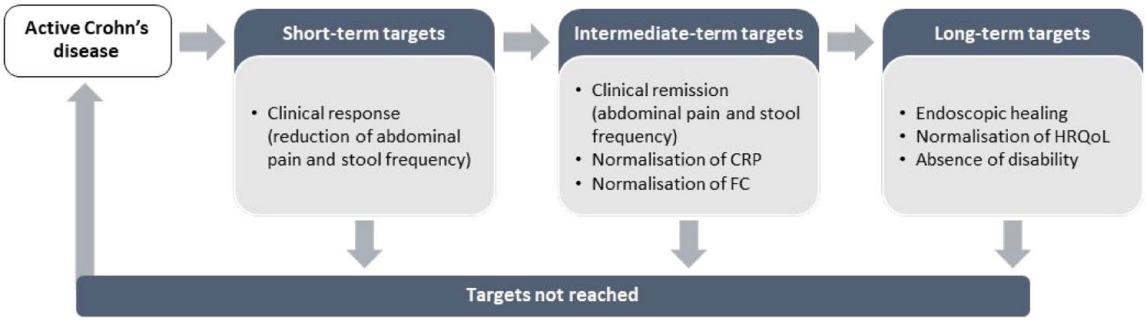

Figure 1. Schematic for treat-to-target approach.
Source: Adapted with permission from Turner et al.[11]
CRP, C-reactive protein; FC, faecal calprotectin; HRQoL, health-related quality of life.

Table 1. STRIDE-II treat-to-target recommendations for patients with CD.

Type	Recommendation
Clinical targets	
Short term	• Clinical response defined as ⩾50% reduction in PRO2 abdominal pain and stool frequency[a,b]
Intermediate term[c]	• Clinical remission defined by PRO2 abdominal pain ⩽1 and stool frequency ⩽3 or HBI <5[a,b]
Endoscopic targets	
Long term[d]	• Endoscopic healing defined by SES-CD <3 or an absence of ulceration[a,e] • Transmural healing is not considered a treatment target but should be used as an adjunct to endoscopic remission
Biomarker targets	
Intermediate term	• Normalisation of CRP to values lower than the upper limit of normal[c] and FC to 100–250 µg/g[a,f]
QoL and disability targets	
Long term	• Normalisation of HRQoL[a] • Absence of disability[a]

Source: Adapted from Turner.[11]
CD, Crohn's disease; CRP, C-reactive protein; FC, faecal calprotectin; HBI, Harvey-Bradshaw index; HRQoL, health-related quality of life; PRO2, the sum of the weighted daily stool frequency and abdominal pain scores from the Crohn's Disease Activity Index; QoL, quality of life; SES-CD, Simple Endoscope Score for Crohn's Disease; STRIDE-II, Selecting Therapeutic Targets in Inflammatory Bowel Disease-II; T2T, treat-to-target.
[a]Consider changing treatment if this target is not achieved.
[b]Time to achieve the target varies by therapy and mechanism of action.
[c]Clinical response and clinical remission are insufficient long-term treatment targets.
[d]Histologic remission is not a treatment target in CD.
[e]Assessed by sigmoidoscopy or colonoscopy or, where infeasible, by capsule endoscopy or balloon enteroscopy.
[f]Thresholds are dependent on the desired outcome. Lower thresholds reflect deep endoscopic, transmural and histological healing, and higher thresholds reflect less stringent outcomes.

released with updated evidence-based targets, accounting for the increase in suggested viable targets provided by emerging treatment and diagnostic options (Table 1).[11] STRIDE-II recommends endoscopic healing as a long-term target for patients with CD, with transmural healing considered an adjunctive measure. Further long-term targets include normalisation of health-related

quality of life (HRQoL) and an absence of disability. Intermediate- or short-term targets include patient-reported response via abdominal pain and stool frequency and normalisation of CRP levels. Clinical remission of abdominal pain and stool frequency, as well as normalisation of CRP and FC levels, are recommended as intermediate targets (Table 1). A recent meta-analysis demonstrated FC as a key predictive measure of endoscopic disease activity in CD, with a pooled sensitivity of 82.4%.[16] Indeed, sustained elevated levels of FC are associated with a risk of relapse, reaching 83% within 2–3 months of initiation (range, 53%–83%).[17] Importantly, FC levels at week 14 are highly predictive of clinical remission within 1 year in individuals treated with anti-tumour necrosis factor (TNF),[18] while targeted FC reduction at ⩽12 weeks after conventional therapy induction has shown favourable long-term prognostic value.[19] Additionally, a retrospective cohort study of 375 patients with CD reported that normalisation of FC by ⩽12 months of being diagnosed was significantly associated with a lower risk of CD progression.[20] Collectively, STRIDE-II considers FC as an important intermediate biomarker of CD.

Importantly, STRIDE-II accommodates individualisation according to safety profiles by careful consideration of the benefit-to-risk ratio of the selected treatment targets. Intensive treatment choices for patients with a low risk of disease progression may incur risks that overshadow the associated treatment benefits.[21] Furthermore, data from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry have shown that infliximab and prednisone use were significant independent predictors of serious infection (both $p \leqslant 0.049$), and prednisone use was a significant independent predictor of mortality ($p < 0.001$).[22] Determining an appropriate T2T approach using the recommended STRIDE-II target must, therefore, consider individual patient profiles, including medical history and comorbidity.

The 2019 National Institute for Health and Care Excellence (NICE) guidelines for managing CD in the United Kingdom recommend initial corticosteroid monotherapy for the induction of remission or budesonide for distal ileal, ileocaecal or right-sided colonic disease where conventional systemic corticosteroids are contraindicated, or in cases where the patient refuses therapy or is corticosteroid intolerant.[23] The current UK clinical practice is also informed by the British Society of Gastroenterology (BSG) guidelines for IBD which do not explicitly define T2T targets.[24] Systemic corticosteroids are recommended for moderate-to-severe CD, and early biologic therapy is recommended for aggressive CD or patients with poor prognostic features (e.g. stricturing).[24]

In a 2022 educational article, the BSG recommended the adoption of the STRIDE-II principles and targets of T2T clinical management.[25] The 2020 European Crohn's and Colitis Organisation (ECCO) guidelines similarly recommend systemic corticosteroids for moderate-to-severe CD and biologics for those who do not respond to conventional therapy.[26] However, despite recommendations for steroids as a starting point for therapy, we recommend close monitoring following their initiation to ensure that patients who do not achieve pre-defined targets are transitioned to potentially more effective or advanced therapy options on time. Consequently, an increased awareness of T2T strategies is required to ensure effective implementation in UK clinical practice.

Challenging treatment targets and the role of patient profiles

While deep healing, defined in STRIDE-II as a combination of clinical remission and complete endoscopic and transmural healing, may be the ultimate treatment goal in CD, the balance of risk-to-benefit ratios and current treatment availability may prevent patients from reaching this goal. Additionally, further research is required to confirm the incremental benefits in patient outcomes gained from attaining deep healing.[11] Nevertheless, selecting challenging targets that surpass symptom control, as outlined in STRIDE-II, may be highly beneficial for certain individuals. Endoscopic healing has been shown to decrease the risk of long-term adverse outcomes.[27,28] In the Randomised Evaluation of an Algorithm for Crohn's Treatment (REACT) study, symptom-guided T2T resulted in a significant reduction in long-term adverse outcomes, including the need for surgery and hospitalisation and serious complications.[29] A systematic literature review conducted in 2015 reported that mucosal healing was associated with long-term clinical remission and a reduced requirement for surgical intervention among patients with CD.[30] Radiological healing, the observable

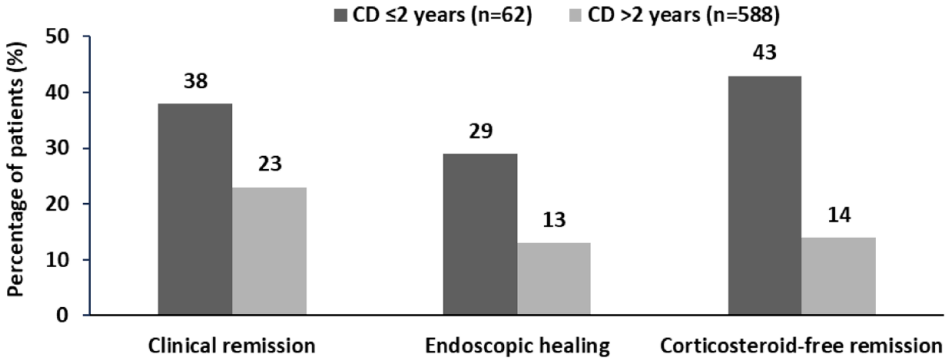

Figure 2. Remission rates at 6 months according to the duration of the CD.
Source: Faleck et al.[39]
$p < 0.05$ on log-rank analyses for all three outcomes. CD, Crohn's disease.

improvement or response identified via several imaging modalities such as magnetic resonance enterography (MRE) and intestinal ultrasound (IUS) have also been suggested as important targets for patients with CD.[31] In STRIDE-II, targets for transmural healing are defined for MRE-based indices such as Magnetic Resonance Index of Activity (MaRIA)[32] <7 points, Clermont index[33] <8.4 or London index[34] <4.1.[11] Guidance for IUS treatment response was provided by leading researchers including those from the International Bowel Ultrasound (IBUS) group, using the RAND/UCLA appropriateness process. In their expert consensus statement, the definition of transmural remission of the small and large bowel in CD was a bowel wall thickness of ⩽3 mm with normal/0 colour Doppler ultrasound signal.[35] A study has indicated that deep healing, defined as a combination of endoscopic and radiological healing, is associated with improved prognosis compared with endoscopic healing only.[36] Furthermore, the radiological response has been significantly associated with a reduction in long-term hospitalisation, CD-related surgery and the need for corticosteroid use among patients with small-bowel CD.[31] Similarly, a retrospective analysis of patients with small-bowel CD indicated the association of radiological response with a decreased rate of surgical or endoscopic intervention; however, hospitalisation rates and treatment adjustments were not affected.[37]

Appropriate treatment targets should be chosen according to individual patient profiles, considering symptoms, prognostic factors and therapy responses.[38] Indeed, disease history and severity may influence the selection of more challenging targets. Patients with a short disease duration have been shown to achieve clinical remission, corticosteroid-free remission and endoscopic response more readily than those with a long disease duration.[39] Consequently, patients with a shorter disease duration may be capable of achieving more ambitious therapeutic targets (Figure 2).[39] Indeed, more ambitious treatment goals may be possible among patients who demonstrate early disease control during initial T2T-based treatment. The ongoing phase 4 CURE trial is exploring sustained deep remission after treatment discontinuation in patients with CD who achieved early disease control with anti-TNF therapy and strict monitoring.[40] The benefits of a T2T approach may, therefore, be expected to be high for patients with a short disease duration without previous treatment failures.[38]

Reasonable targets for patients where complete remission is not achievable

With more therapeutic options available, many patients can achieve complete remission; however, for some, this is not a realistic goal, and therefore 'reasonable' targets should be selected to provide optimal clinical care in this patient population. For example, targeting and accepting a low disease activity state may be appropriate for certain patients, such as those with longstanding disease, multiple prior treatment experiences and/or bowel resections. Indeed, an important long-term goal in STRIDE-II is the normalisation of HRQoL, an outcome associated with sustained long-term remission when achieved at 14 weeks.[11,41] HRQoL is impacted by various factors, which individually may serve as more

reasonable targets among certain patients. High rates of both anxiety and depression have been associated with IBD, including CD, particularly during active phases of the disease, and may be individually targeted to improve HRQoL.[42] Fatigue is also strongly associated with poor HRQoL and may be readily screened throughout the course of T2T-based treatment.[43] Finally, sexual dysfunction significantly affects HRQoL in patients with IBD, with specific independent predictors, including the use of corticosteroids among women and the use of biologic agents and concurrent diabetes among men.[44] T2T strategies may, therefore, consider treatment choices accordingly, such as via associated comorbidities that influence HRQoL.

Potential future targets

Lowering faecal lactoferrin (FL) levels and ultrasound remission are two targets that have also been assessed. In a post hoc analysis of the UNIFI and PURSUIT trials, high levels of FL at week 4 were significantly associated with lower likelihoods of clinical remission, endoscopic improvement and endoscopic remission.[45] However, FL is not widely available or used in UK clinical practice. Another prospective cohort study reported that achieving ultrasound remission (Bowel Ultrasound Score (BUSS) $\leqslant$3.52) was the sole predictor for long-term endoscopic remission in patients with CD. Having a BUSS $>$3.52 at week 12 was associated with not reaching lasting endoscopic remission.[46]

Patient voice for selecting treatment targets

The STRIDE-II guidelines should be collaboratively discussed with the patient. Patient perspectives on the shift toward a T2T approach have generally not been widely incorporated into CD treatment, including within the United Kingdom. Indeed, the BSG and ECCO have not incorporated T2T recommendations into their respective guidelines to date.[10,24,26,47] Recent findings on T2T-related patient view for CD treatment focusing on acceptability and specific targets have shown that almost 70% of patients in clinical remission agreed to T2T, with reductions in the risk of flare, hospitalisation, surgery and colorectal cancer considered the most acceptable goals.[48] Interestingly, although most demographic and clinical characteristics were non-predictive of patient acceptance, second-line anti-TNF treatment was linked to a lower likelihood of acceptance, possibly due to prior treatment failures and difficulty managing CD.[48]

Shared decision-making (SDM) among clinicians and patients is crucial for establishing individualised T2T to incorporate patient-reported outcomes (PROs) and patient-specified treatment goals. However, the significant divergence between clinician and patient perspectives may reduce the feasibility of attaining T2T outcomes, such as complete symptom resolution and mucosal normalisation. For example, patients may be unwilling to escalate therapy if the current treatment is perceived to enable personal goals (such as improved social functioning and HRQoL) rather than other T2T outcomes (such as complete symptom resolution and mucosal healing). By contrast, a cohort study of 298 patients with IBD revealed that a majority of the patients were willing to accept significant risks to maintain disease control.[48] Another study evaluating treatment choices between patients participating in SDM versus standard patient education reported that a significantly higher number of patients chose combination therapy over the standard of care in the group that participated in SDM versus the group that did not.[49] Balancing the risks and benefits of a T2T treatment plan should, thus, be an integral part of the clinician–patient collaboration for selecting appropriate targets and goals.

In clinical practice, giving equal weight to patient and clinician perspectives allows the patient to take ownership of their treatment plan. Importantly, although more extensive patient control of treatment has been described in fields such as dermatology,[50,51] the volume of CD-related information might be difficult to assimilate in daily clinical practice. Patient decision aids, among other forms of patient support, may help to guide decision-making. Patients are, however, often influenced by clinician recommendations or their multidisciplinary team (MDT) and may require encouragement or support to ensure that their voice is heard. Crohn's & Colitis UK has developed a range of resources and tools to assist HCPs with patient engagement, including focus groups, surveys and service open days (Table 2).[52] The AWARE-IBD project has developed an accessible toolkit in a wide range of languages to support more confident communication between patients with IBD and

Table 2. Patient involvement resources (from Crohn's and Colitis).

Format	Description
User panels and reference groups	• Provide a sounding board and advice on service redesign, development and research. • Proactively offer suggestions for future developments and current service improvements. • Inform and empower patients, carers and families.
Focus groups	• Explore a variety of issues and test solutions. • Explore group perspectives of a problem and generate ideas. • Discover the true thoughts and feelings regarding a topic or service.
Process mapping	• Assist HCP to understand the patient's perspective of care. • Illustrate the patient journey through service from diagnosis to primary care, inpatient and outpatient services. • Identify gaps or pinch points in the system.
Surveys, questionnaires and interviews	• Obtain patient views and ideas for improvement and identify patient views of a service, including the proposed changes.
Digital stories	• Powerful first-person narratives that can combine images, music or video clips into a short video (usually 2–5 min).
World café	• Assist with generating ideas and solutions for challenging issues. • A stand-alone event or part of a larger event. • Participants are encouraged to share and build their stories in small groups, allowing individuals to speak or listen. Linking several group conversations assists with identifying common themes and new insights.
Emotional touchpoints	• Refer to key moments or events in an individual's experience receiving or delivering a service, as individuals tend to recall specific emotions or deep, lasting memories of particular aspects of a service.
Service open days	• A free event that provides parents, carers and newly diagnosed patients with an opportunity to meet with the healthcare team. Patients have an opportunity to discuss their experiences and suggest service improvements. May identify individuals interested in participating in service development.

HCP, healthcare professional.

their treating health team.[53] Importantly, patient preferences may differ from those of clinicians.[54] A personalised care plan may, thus, also help understand what matters to an individual and is recommended in IBD UK standards.[55]

Improved treatment target prediction using combined disease markers

Combining multiple disease markers has been shown to further improve the accuracy of predicting treatment targets. In the CALM study, combining CRP with FC was a superior predictor of endoscopic healing after 48 weeks of adalimumab treatment than FC alone.[56] In the paediatric ImageKids cohort, the Mucosal-Inflammation-Non-Invasively index combined with CRP and FC exhibited better performance in indicating endoscopic inflammation than when combined with FC alone.[57] Similarly, the performance of the Utrecht Activity Index in predicting endoscopic activity was shown to be increased when combined with both CRP and FC than FC alone in adults.[58]

Identification of primary or secondary first-line treatment failure

Patients exhibiting first-line treatment failure are broadly categorised into primary non-responders who experience an initial non-response to induction therapy and secondary non-responders who lose response after demonstrating an initial response.[59]

Primary non-responders

In clinical practice, STRIDE-II recommends the prompt identification of both primary and secondary non-responders via close endoscopic and PRO monitoring of treatment response. However, repeated endoscopy may not be feasible or may differ across routine clinical practice in the United Kingdom. For example, endoscopic evaluation may be limited by several barriers such as capacity issues in healthcare centres and patient reluctance to undergo colonoscopy. Clinician preference may also influence monitoring choices; for example, magnetic resonance imaging (MRI) is considered a reliable modality.[60] Regardless of the monitoring approach used (i.e. endoscopy, MRI or ultrasound), close follow-up of patients is recommended. A 14-week timeline with scheduled routine assessments is expected to be a sufficient period to identify primary non-response in clinical practice[61]; in the UK-wide Personalised Anti-TNF therapy in Crohn's Disease (PANTS) study, primary non-response occurred in almost a quarter of patients with CD when assessed after induction.[62] However, it is important to consider the variable time-to-response associated with different therapies. For example, in a prospective, observational, cohort study of 136 patients with IBD, of whom 94 had CD, clinical response to vedolizumab was shown by week 14 in 58% of patients with CD disease activity at baseline ($N=55$).[63] In another observational cohort study, complete or partial response to adalimumab was observed as early as week 4 in 55.6% and 42.1% of patients with CD ($N=126$), respectively.[64]

Partial responders

Partial primary response is where despite symptomatic and biochemical remission, imaging results demonstrate continued active inflammation.[65] Clinical indications of partial response must be assessed at timepoints defined by the specific induction therapy administered. The partial response may be improved through medication dose escalation or a switch to an alternative therapy.[65] Indeed, retrospective observational data have shown that escalating the dose frequency of ustekinumab in non-responders (active disease at 16 weeks from induction; $n=15$) to once every 4 weeks (Q4W) from the standard once every 8 weeks (Q8W) improved clinical outcomes, as indicated by a decreased Physician Global Assessment disease severity score, decreased CRP levels, prevention of an increase in CRP levels and increased serum albumin levels.[66] The UK Licence states that, for patients who lose response on the standard once-every-12-week dosing of ustekinumab, an increased dosing frequency of Q8W may be beneficial; however, if no evidence of therapeutic benefit is seen after 16 weeks of IV induction or 16 weeks after switching to a Q8W maintenance dose, discontinuation should be considered.[67] If treatment escalation fails to improve clinical activity, switching out of class is recommended, as in-class switching to options with similar mechanisms of action is likely to be insufficient, except in the setting of demonstrably low plasma drug levels with or without the presence of antidrug antibodies.[68] Studies investigating biologic therapies have also shown improved clinical outcomes among inadequate responders following dose escalation, although the optimal timepoint for escalation is unclear.[69,70]

Secondary non-responders

For treatment responders, routine symptomatic and laboratory monitoring should be employed to evaluate subsequent loss of response.

STRIDE-II applied the two-item PRO Mayo score (PRO2), a weighted summed measure of stool frequency and abdominal pain items from the CD activity index, as a measure of clinical response and remission.[11] Several other PRO-based measures are also available or are under development for IBD in the United Kingdom. The True Colours' self-management system prompts patients to regularly report symptoms by text messages or a web interface.[71] Visually effective symptom summaries, such as the CD Life Index Questionnaire and Helpline/Toolkit, provide patients with direct insights into their health and clinicians with continuous high-frequency symptom data between visits. Recommendations from the BSG guidelines suggest that annual reviews should be conducted for patients using biologics at home.[24]

Endoscopy and MRI are commonly utilised, while inflammatory biomarkers may be used to prompt further investigation with these modalities. As a cost-effective and non-invasive measure of inflammation,[72] FC may be utilised to complement endoscopic follow-up.[73] Importantly, in the phase 3 CALM study of early CD, treatment strategies based on a tightly controlled algorithm of clinical symptoms plus FC and CRP levels resulted in

superior rates of mucosal healing compared with those based on symptoms alone.[13] However, biomarkers can be used for accurate disease monitoring only if they correlate well with endoscopic, radiographic and histologic evaluations. In a systematic review, CRP had only 49% sensitivity to endoscopically active CD, whereas FC showed 87% sensitivity.[74,75] Therefore, individual sequential assessment of FC should be considered to determine the disease's 'direction of change'.

Timely identification of secondary loss of response is important to allow early treatment or dose escalation or a switch of drug class. In the CALM study, timely adalimumab escalation afforded by the tight control group was associated with improved clinical outcomes compared with the conventional management group.[13] The REACT study showed that, although CD remission was not impacted, early combined immunosuppression therapy and therapy switching allowed for a reduction in adverse clinical outcomes.[29] Proactive drug monitoring may be an important strategy for the early recognition and management of a loss of response, as proactive drug monitoring among patients with IBD has led to shorter intervals of therapy escalation than reactive monitoring.[76]

Reporting outcomes of endoscopy

Endoscopic scoring systems are encouraged for reporting CD outcomes in clinical practice, as they align management with available literature and enable comparisons across treatment centres or between serial endoscopies in an individual patient.[77,78] Of the several quantitative endoscopy healing scores available (Table 3), STRIDE-II recommends giving strong consideration to the use of the Simple Endoscopic Score for Crohn's Disease (SES-CD), a simplified version of the CD Endoscopic Index of Severity (CDEIS). The SES-CD assesses ileocolonic segments (rectum, sigmoid/left colon, transverse colon, right colon and ileum), ulcer size, ulcerated surface, affected surface and the presence of stenosis to provide a sum score ranging from 0 to 56,[79] with a higher score denoting higher mucosal disease activity.[80] Although certain clinicians may consider formal endoscopy scores impractical due to their perceived complexity or a lack of associated formal training, we recommend reporting individual items per ileocolonic segment, in lieu of the numeric score. As a practical scoring system, the SES-CD is also recommended by the BSG guidelines and has been shown to help predict treatment outcomes in a real-world observational UK cohort.[24,81] In centres where SES-CD scoring is not performed, the resolution of ulceration could be used as an easily defined and assessed treatment target. This, however, lacks the granularity to establish a clinically meaningful threshold of response and may not reveal persisting microscopic disease.[82]

Table 3. Endoscopic scoring systems.[83]

Index	Description	Endoscopic activity score categories
CDEIS[84,85]	Five pre-defined segments of the intestine (ileum, right colon, transverse colon, left/sigmoid colon and rectum) are assessed according to the following parameters: superficial ulcerations (score: 6), deep ulcerations (score: 12), segmental surface involved by disease (score: 0–10) and surfaced ulcerated (score: 0–10). The summed score is divided by the total number of segments assessed. An additional score of 3 is added to the result if stenosis is detected, regardless of its relation to ulceration.	• Inactive (remission): <3 • Mild: 3–8 • Moderate: $\geqslant$9–12 • Severe: $\geqslant$13
SES-CD[80,86]	Developed as a simplified alternative to the CDEIS, patients are assessed according to ulcer presence or size (0–3), ulcerated surface (0–3), affected surface (0–3) and stenosis (0–3). A strong correlation has been shown with the CDEIS ($r=0.920$), clinical parameters and serum levels of CRP.	• Inactive: 0–2 • Mild: 3–6 • Moderate: 7–15 • Severe: >16

(Continued)

Table 3. (Continued)

Index	Description	Endoscopic activity score categories
Rutgeerts score[87]	Developed to assess post-surgical disease activity and the severity of post-surgical endoscopic lesions at the ileocolic anastomosis level.	• No lesions: i0 • 1–5 anastomotic aphthous lesions: i1 • 2 to >5 aphthous lesions with normal mucosa between or skip areas of larger lesions/ulcers confined to ileocolonic anastomosis (<1 cm): i2 • Diffuse aphthous ileitis with diffusely inflamed mucosa: i3 • Diffuse inflammation, with larger lesions: large ulcers, nodules and/or narrowing: i4

CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Clinicians should consider scoring systems for assessing both objective and subjective remission endpoints, including the measures of quality of life. Several disease activity indices have been validated for assessing radiological activity via MRI and ultrasound.[88,89] Importantly, radiological activity is commonly considered descriptive, subjective and qualitative and, thus, lacks the objectivity of a formal, quantifiable disease activity index. However, these descriptive radiological assessments provide valuable information regarding activity progression or regression and important disease-related complications such as stricture formation, pre-stenotic dilatation and penetration.[90] Radiological reassessment can thus be used as a treatment target, either by targeting complete normalisation or a low disease activity state. Additionally, patients' quality of life may be subjectively assessed via scores such as the IBD-Control measure, which has been validated as a simple and time-efficient measure that may support routine monitoring.[91]

Follow-up beyond 1 year

Patients who continue therapy require regular and long-term follow-up and monitoring. Because of the poor correlation between clinical symptoms and disease activity, symptom monitoring alone is insufficient.[92] However, the optimal timing for endoscopic monitoring is unclear.[93] Therefore, follow-up procedures vary across clinical practice in the United Kingdom. Biomarker monitoring of FC and CRP is recommended every 6–12 months for patients in remission and every 2–4 months for patients with active CD.[94] Further assessments at specific points such as during disease flares and initiation or cessation of medication have also been used.[72] Although clinical symptoms correlate poorly with disease activity, PROs may serve as long-term (⩾48 weeks) key indicators of the qualitative measures of disease from the patient's perspective.[95,96]

Important role of the MDT

In UK clinical practice, the IBD MDT approach supports the provision of optimised and personalised care, including monitoring of a T2T strategy.[24,97,98] The IBD MDT should include a core team consisting of gastroenterologist, colorectal surgeon, IBD specialist nurse, radiologist, administrative support, dietitian, histopathologist and pharmacist.[24] The BSG guidelines recommend that MDT meetings should occur at an adequate frequency to prevent delays in decision-making and have the capacity to handle the case load.[24] Structured eligibility criteria should be used for case selection, discussion and appropriate scheduling.[99] The MDT should adopt a patient-centred approach that considers patient preferences and convenience.[100] In addition, patients should be provided with information and support at all disease stages to enable SDM with the MDT,[101] especially those requiring surgical management.[102,103] In smaller centres, the IBD MDT may be part of an overall gastroenterology MDT.

Some UK IBD centres also have a biologics committee or virtual biologics clinic or meeting to review patients escalating to biologic therapy or switching. This review may include a 'checklist' to ensure alignment with funding agreements and that appropriate pre-treatment screening is undertaken. Recently, a survey highlighted the importance of multidisciplinary biologics-focused

committees, which revealed substantial heterogeneity in the practical use and interpretation of therapeutic drug monitoring for informing biologic treatment choices among patients with IBD.[104]

Conclusion

This article summarises best practice recommendations from the STRIDE-II guidelines for implementing T2T-based goals for CD treatment in UK clinical practice. However, rather than provide operational guidance on the implementation of the guidelines, this was an attempt to introduce a conceptual framework that could be used by clinicians specifically in the United Kingdom to integrate STRIDE-II guidelines into their working circumstances.

Over the last decade, the CD treatment paradigm has shifted significantly from symptom control toward a goal-directed, patient-informed treatment strategy. Within the United Kingdom, the current guidelines informing clinical practice do not incorporate detailed recommendations for T2T approaches. Patient goals should inform T2T approaches. This article presents the applicability of the recent STRIDE-II guidelines, which recommend CD treatment according to pre-defined targets, including endoscopic healing, normalisation of serum and faecal biomarkers, restoration of HRQoL and absence of disability, all of which are facets of sustained clinical remission. Evidence supports the chosen targets in STRIDE-II, with a growing patient acceptance of this approach. Education-based efforts are required to further highlight the benefits of T2T approaches for the management of CD and other IBDs.

Declarations

Job number: C-APROM/GB/ENTCD/0003
Date of prep: November 2024

Entyvio (vedolizumab) prescribing information (PI) can be found at https://www.emcpi.com/grp/57. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Takeda at AE.GBR-IRL@takeda.com

Ulcerative colitis

Entyvio (vedolizumab) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or an anti-tumour necrosis factor-alpha (TNFα) therapy.

Crohn's disease

Entyvio (vedolizumab) is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or an anti-tumour necrosis factor-alpha (TNFα) therapy.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Karen Kemp: Conceptualisation; Writing – review & editing.

Mark A. Samaan: Conceptualisation; Writing – review & editing.

Ajay M. Verma: Conceptualisation; Writing – review & editing.

Alan J. Lobo: Conceptualisation; Writing – review & editing.

Acknowledgements

This article was initiated and funded by Takeda UK Ltd. Medical writing support was provided by Rebecca Watkin, PhD; Varsha Jain, PhD; Shruti Muralidharan, PhD; and Adityadeb Ghosh, M. Pharm of Cactus Life Sciences and was funded by Takeda UK Ltd.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This article was initiated and funded by Takeda UK Ltd.

Competing interests

KK reports speaker fees from AbbVie, Celltrion, Ferring, Galapagos, Janssen, Takeda and Tillotts and for other educational activities from AbbVie, Galapagos, Takeda, Tillotts. MS reports advisory fees from AbbVie, Bristol-Myers Squibb, Galapagos, Janssen, Sandoz, Samsung Bioepis, Takeda and Tillotts, as well as lecture fees from AbbVie, Bristol-Myers Squibb, Falk, Galapagos,

Janssen, MSD and Takeda. AV reports research grants from Thermo Fisher Scientific; speaker fees from AbbVie, Celltrion, Ferring, Takeda and UCB pharma limited; and for other educational activities from AbbVie, Celltrion, Galapagos NV, Takeda and Tillotts. AL reports speaker and consulting fees from Bristol-Myers Squibb, Celltrion, Ferring, Janssen, Medtronic, Pfizer, Takeda and Vifor Pharma and for other educational activities from Celltrion.

Availability of data and materials

Not applicable.

ORCID iD

Karen Kemp https://orcid.org/0000-0002-4528-6319

References

1. Torres J, Mehandru S, Colombel JF, et al. Crohn's disease. *Lancet* 2017; 389: 1741–1755.
2. Feuerstein JD and Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. *Mayo Clin Proc* 2017; 92: 1088–1103.
3. Thompson NP, Fleming DM, Charlton J, et al. Patients consulting with Crohn's disease in primary care in England and Wales. *Eur J Gastroenterol Hepatol* 1998; 10: 1007–1012.
4. Christensen B, Erlich J, Gibson PR, et al. Histologic healing is more strongly associated with clinical outcomes in ileal Crohn's disease than endoscopic healing. *Clin Gastroenterol Hepatol* 2020; 18: 2518–2525.e1.
5. Sulz MC, Burri E, Michetti P, et al. Treatment algorithms for Crohn's disease. *Digestion* 2020; 101 Suppl 1: 43–57.
6. Garcia NM, Cohen NA and Rubin DT. Treat-to-target and sequencing therapies in Crohn's disease. *United Eur Gastroenterol J* 2022; 10: 1121–1128.
7. Gracie DJ, Williams CJ, Sood R, et al. Poor correlation between clinical disease activity and mucosal inflammation, and the role of psychological comorbidity, in inflammatory bowel disease. *Am J Gastroenterol* 2016; 111: 541–551.
8. Colombel JF, D'haens G, Lee WJ, et al. Outcomes and strategies to support a treat-to-target approach in inflammatory bowel disease: a systematic review. *J Crohns Colitis* 2020; 14: 254–266.
9. West J, Tan K, Devi J, et al. Benefits and challenges of treat-to-target in inflammatory bowel disease. *J Clin Med* 2023; 12: 6292.
10. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015; 110: 1324–1338.
11. Turner D, Ricciuto A, Lewis A, 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: 1570–1583.
12. Ungaro RC, Yzet C, Bossuyt P, et al. Deep remission at 1 year prevents progression of early Crohn's disease. *Gastroenterology* 2020; 159: 139–147.
13. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2017; 390: 2779–2789.
14. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; 385: 1406–1417.
15. Bouguen G, Levesque BG, Pola S, et al. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014; 12: 978–985.
16. Rokkas T, Portincasa P and Koutroubakis IE. Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis. *J Gastrointestin Liver Dis* 2018; 27: 299–306.
17. Heida A, Park KT and van Rheenen PF. Clinical utility of fecal calprotectin monitoring in asymptomatic patients with inflammatory bowel disease: a systematic review and practical guide. *Inflamm Bowel Dis* 2017; 23: 894–902.
18. Boschetti G, Garnero P, Moussata D, et al. Accuracies of serum and fecal S100 proteins (calprotectin and calgranulin C) to predict the response to TNF antagonists in patients with Crohn's disease. *Inflamm Bowel Dis* 2015; 21: 331–336.
19. Haisma SM, Verkade HJ, Scheenstra R, et al. Time-to-reach target calprotectin level in newly diagnosed patients with inflammatory bowel

disease. *J Pediatr Gastroenterol Nutr* 2019; 69: 466–473.

20. Plevris N, Fulforth J, Lyons M, et al. Normalization of fecal calprotectin within 12 months of diagnosis is associated with reduced risk of disease progression in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2021; 19: 1835–1844 e6.
21. Siegel CA and Bernstein CN. Identifying patients with inflammatory bowel diseases at high vs low risk of complications. *Clin Gastroenterol Hepatol* 2020; 18: 1261–1267.
22. Lichtenstein GR, Feagan BG, Cohen RD, et al. Infliximab for Crohn's disease: more than 13 years of real-world experience. *Inflamm Bowel Dis* 2018; 24: 490–501.
23. National Institute for Health and Care Excellence (NICE). Crohn's disease: management (NG129), https://www.nice.org.uk/guidance/ng129 (2019, accessed 18 March 2024).
24. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; 68: s1–s106.
25. Chatten K, Limdi J and Selinger C. Corticosteroids in the management of inflammatory bowel disease, https://www.bsg.org.uk/web-education-articles-list/corticosteroids-in-the-management-of-inflammatory-bowel-disease/ (2022, accessed 18 March 2024).
26. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020; 14: 4–22.
27. Yzet C, Diouf M, Le Mouel JP, et al. Complete endoscopic healing associated with better outcomes than partial endoscopic healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2020; 18: 2256–2261.
28. Peyrin-Biroulet L. Mucosal healing in Crohn's disease and ulcerative colitis. *Gastroenterol Hepatol (N Y)* 2020; 16: 206–208.
29. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet* 2015; 386: 1825–1834.
30. Shah SC, Colombel JF, Sands BE, et al. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; 43: 317–333.
31. Deepak P, Fletcher JG, Fidler JL, et al. Radiological response is associated with better long-term outcomes and is a potential treatment target in patients with small bowel Crohn's disease. *Am J Gastroenterol* 2016; 111: 997–1006.
32. Rimola J, Rodriguez S, Garcia-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. *Gut* 2009; 58: 1113–1120.
33. Buisson A, Joubert A, Montoriol PF, et al. Diffusion-weighted magnetic resonance imaging for detecting and assessing ileal inflammation in Crohn's disease. *Aliment Pharmacol Ther* 2013; 37: 537–545.
34. Steward MJ, Punwani S, Proctor I, et al. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. *Eur J Radiol* 2012; 81: 2080–2088.
35. Ilvemark J, Hansen T, Goodsall T, et al. Defining transabdominal intestinal ultrasound treatment response and remission in inflammatory bowel disease: systematic review and Expert Consensus Statement. *J Crohns Colitis* 2022; 16: 554–580.
36. Oh K, Oh EH, Noh SM, et al. Combined endoscopic and radiologic healing is associated with a better prognosis than endoscopic healing only in patients with Crohn's disease receiving anti-TNF therapy. *Clin Transl Gastroenterol* 2022; 13: e00442.
37. Halle E, Azahaf M, Duveau N, et al. Radiological response is associated with better outcomes and should be considered a therapeutic target in Crohn's disease. *Dig Dis Sci* 2020; 65: 2664–2674.
38. Sandborn WJ, Hanauer S, Van Assche G, et al. Treating beyond symptoms with a view to improving patient outcomes in inflammatory bowel diseases. *J Crohns Colitis* 2014; 8: 927–935.
39. Faleck DM, Winters A, Chablaney S, et al. Shorter disease duration is associated with higher rates of response to vedolizumab in patients with Crohn's disease but not ulcerative colitis. *Clin Gastroenterol Hepatol* 2019; 17: 2497–2505.e1.
40. ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine (US). Identifier NCT03306446, Changing the coUrse of cRohn's disease with an early use of adalimumab (CURE); 31 May 2023 [cited 18 March 2024]; [about 5 screens], https://clinicaltrials.gov/study/NCT03306446 (2017).
41. Herrera-deGuise C, Casellas F, Robles V, et al. Predictive value of early restoration of quality

of life in Crohn's disease patients receiving antitumor necrosis factor agents. *J Gastroenterol Hepatol* 2015; 30: 286–291.

42. Mikocka-Walus A, Knowles SR, Keefer L, et al. Controversies revisited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis* 2016; 22: 752–762.
43. Cohen BL, Zoëga H, Shah SA, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther* 2014; 39: 811–822.
44. Marín L, Mañosa M, Garcia-Planella E, et al. Sexual function and patients' perceptions in inflammatory bowel disease: a case-control survey. *J Gastroenterol* 2013; 48: 713–720.
45. Chen R, Tie Y, Zhang X, et al. Fecal lactoferrin early predicts long-term outcomes in ulcerative colitis: a post-hoc analysis of the UNIFI and PURSUIT trials. *United Eur Gastroenterol J* 2023; 11: 542–550.
46. Allocca M, Dell'Avalle C, Zilli A, et al. Ultrasound remission after biologic induction and long-term endoscopic remission in Crohn's disease: a prospective cohort study. *EClinicalMedicine* 2024; 71: 102559.
47. Doherty G, Katsanos KH, Burisch J, et al. European Crohn's and Colitis Organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J Crohns Colitis* 2018; 12: 17–31.
48. Selinger C, Carbonell J, Kane J, et al. Acceptability of a 'treat to target' approach in inflammatory bowel disease to patients in clinical remission. *Frontline Gastroenterol* 2021; 12: 30–38.
49. Zisman-Ilani Y, Thompson KD, Siegel LS, et al. Crohn's disease shared decision making intervention leads to more patients choosing combination therapy: a cluster randomised controlled trial. *Aliment Pharmacol Ther* 2023; 57: 205–214.
50. Morrison T, Johnson J, Baghoomian W, et al. Shared decision-making in dermatology: a scoping review. *JAMA Dermatol* 2021; 157: 330–337.
51. Tan J, Linos E, Sendelweck MA, et al. Shared decision making and patient decision aids in dermatology. *Br J Dermatol* 2016; 175: 1045–1048.
52. Crohn's & Colitis UK. Patient involvement tools and resources for healthcare professionals, https://crohnsandcolitis.org.uk/our-work/campaigns/improving-your-healthcare/involving-people-with-crohn-s-and-colitis-in-improving-healthcare/patient-involvement-tools-and-resources-for-healthcare-professionals (accessed 18 March 2024).
53. Voice Ability. Aware-IBD self-advocacy toolkit, https://www.voiceability.org/support-and-help/services-in-your-area/aware-ibd (accessed 18 March 2024).
54. Al Khoury A, Balram B, Bessissow T, et al. Patient perspectives and expectations in inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2022; 67: 1956–1974.
55. IBD UK. IBD standards, https://ibduk.org/ibd-standards (accessed 18 March 2024).
56. Reinisch W, Panaccione R, Bossuyt P, 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: 1562–1571.
57. Cozijnsen MA, Ben Shoham A, Kang B, et al. Development and validation of the mucosal inflammation noninvasive index for pediatric Crohn's disease. *Clin Gastroenterol Hepatol* 2020; 18: 133–140 e1.
58. Minderhoud IM, Steyerberg EW, van Bodegraven AA, et al. Predicting endoscopic disease activity in Crohn's disease: a new and validated noninvasive disease activity index (the Utrecht Activity Index). *Inflamm Bowel Dis* 2015; 21: 2453–2459.
59. Papamichael K, Gils A, Rutgeerts P, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. *Inflamm Bowel Dis* 2015; 21: 182–197.
60. Rozendorn N, Amitai MM, Eliakim RA, et al. A review of magnetic resonance enterography-based indices for quantification of Crohn's disease inflammation. *Therap Adv Gastroenterol* 2018; 11: 1756284818765956.
61. Marsal J, Barreiro-de Acosta M, Blumenstein I, et al. Management of non-response and loss of response to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Front Med (Lausanne)* 2022; 9: 897936.
62. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019; 4: 341–353.

63. Christensen B, Colman RJ, Micic D, et al. Vedolizumab as induction and maintenance for inflammatory bowel disease: 12-month effectiveness and safety. *Inflamm Bowel Dis* 2018; 24: 849–860.
64. Saro C, Ceballos D, Muñoz F, et al. Clinical status, quality of life, and work productivity in Crohn's disease patients after one year of treatment with adalimumab. *Rev Esp Enferm Dig* 2017; 109: 122–129.
65. Iijima H, Kobayashi T, Nagasaka M, et al. Management of primary nonresponders and partial responders to tumor necrosis factor-α inhibitor induction therapy among patients with Crohn's disease. *Inflamm Intest Dis* 2020; 5: 78–83.
66. Haider SA, Yadav A, Perry C, et al. Ustekinumab dose escalation improves clinical responses in refractory Crohn's disease. *Therap Adv Gastroenterol* 2020; 13: 1756284820959245.
67. Janssen-Cilag International NV. *STELARA (summary of product characteristics)*. Belgium: Janssen-Cilag International NV, 2013.
68. Dalal SR and Cohen RD. What to do when biologic agents are not working in inflammatory bowel disease patients. *Gastroenterol Hepatol (N Y)* 2015; 11: 657–665.
69. Meserve J, Ma C, Dulai PS, et al. Effectiveness of reinduction and/or dose escalation of ustekinumab in Crohn's disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2022; 20: 2728–2740 e1.
70. Mattoo VY, Basnayake C, Connell WR, et al. Systematic review: efficacy of escalated maintenance anti-tumour necrosis factor therapy in Crohn's disease. *Aliment Pharmacol Ther* 2021; 54: 249–266.
71. True colours self-management system, https://oxfordhealth.truecolours.nhs.uk/www/en/ (accessed 18 March 2024).
72. Plevris N and Lees CW. Disease monitoring in inflammatory bowel disease: evolving principles and possibilities. *Gastroenterology* 2022; 162: 1456–1475 e1.
73. Røseth AG, Fagerhol MK, Aadland E, et al. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. *Scand J Gastroenterol* 1992; 27: 793–798.
74. Ma C, Battat R, Khanna R, et al. What is the role of C-reactive protein and fecal calprotectin in evaluating Crohn's disease activity? *Best Pract Res Clin Gastroenterol* 2019; 38-39: 101602.
75. Lasson A, Stotzer PO, Öhman L, et al. The intra-individual variability of faecal calprotectin: a prospective study in patients with active ulcerative colitis. *J Crohns Colitis* 2015; 9: 26–32.
76. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab. *Clin Gastroenterol Hepatol* 2017; 15: 1580–1588 e3.
77. Ket SN, Palmer R and Travis S. Endoscopic disease activity in inflammatory bowel disease. *Curr Gastroenterol Rep* 2015; 17: 50.
78. Kim KO. Endoscopic activity in inflammatory bowel disease: clinical significance and application in practice. *Clin Endosc* 2022; 55: 480–488.
79. Gottlieb K, Daperno M, Usiskin K, et al. Endoscopy and central reading in inflammatory bowel disease clinical trials: achievements, challenges and future developments. *Gut* 2021; 70: 418–426.
80. Daperno M, D'haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; 60: 505–512.
81. Meade S, Routledge E, Sharma E, et al. How achievable are STRIDE-II treatment targets in real-world practice and do they predict long-term treatment outcomes? *Frontline Gastroenterol* 2023; 14: 312–318.
82. Walsh A, Palmer R and Travis S. Mucosal healing as a target of therapy for colonic inflammatory bowel disease and methods to score disease activity. *Gastrointest Endosc Clin N Am* 2014; 24: 367–378.
83. IG-IBD. IG-IBD scores – calculators in gastroenterology, https://www.igibdscores.it/app/en/ (accessed 18 March 2024).
84. Mary JY and 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: 983–989.
85. Sipponen T, Savilahti E, Kolho KL, et al. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008; 14: 40–46.
86. Koutroumpakis E and Katsanos KH. Implementation of the simple endoscopic activity

score in Crohn's disease. *Saudi J Gastroenterol* 2016; 22: 183–191.

87. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; 99: 956–963.

88. D'Amico F, Chateau T, Laurent V, et al. Which MRI score and technique should be used for assessing Crohn's disease activity? *J Clin Med* 2020; 9: 1691.

89. Freitas M, de Castro FD, Macedo Silva V, et al. Ultrasonographic scores for ileal Crohn's disease assessment: Better, worse or the same as contrast-enhanced ultrasound? *BMC Gastroenterol* 2022; 22: 252.

90. Nancey S, Fumery M, Faure M, et al. Use of imaging modalities for decision-making in inflammatory bowel disease. *Therap Adv Gastroenterol* 2023; 16: 17562848231151293.

91. Bodger K, Ormerod C, Shackcloth D, et al. Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. *Gut* 2014; 63: 1092–1102.

92. Soleymani S, Moradkhani A, Eftekhari M, et al. Correlation between clinical symptoms and lab tests with endoscopic severity indexes in patients with inflammatory bowel diseases. *Middle East J Dig Dis* 2020; 12: 162–170.

93. Kucharzik T, Verstockt B and Maaser C. Monitoring of patients with active inflammatory bowel disease. *Front Gastroenterol* 2023; 2: 1172318.

94. Ananthakrishnan AN, Adler J, Chachu KA, et al. AGA Clinical Practice Guideline on the role of biomarkers for the management of Crohn's disease. *Gastroenterology* 2023; 165: 1367–1399.

95. Tran F, Schirmer JH, Ratjen I, et al. Patient reported outcomes in chronic inflammatory diseases: current state, limitations and perspectives. *Front Immunol* 2021; 12: 614653.

96. Janssen LM, Creemers RH, van Bodegraven AA, et al. A systematic review on long-term efficacy outcome measures in Crohn's disease patients. *J Crohns Colitis* 2023; 17: 1528–1536.

97. Crohn's & Colitis UK. Who is in an IBD team?, https://crohnsandcolitis.org.uk/our-work/healthcare-professionals/build-an-ibd-team/who-is-in-an-ibd-team (accessed 18 March 2024).

98. National Institute for Health and Care Excellence (NICE). Inflammatory bowel disease–quality standard [QS81] – quality statement 2: multidisciplinary team support, https://www.nice.org.uk/guidance/qs81/chapter/quality-statement-2-multidisciplinary-team-support (accessed 18 March 2024).

99. Morar P, Read J, Arora S, et al. Defining the optimal design of the inflammatory bowel disease multidisciplinary team: results from a multicentre qualitative expert-based study. *Frontline Gastroenterol* 2015; 6: 290–297.

100. Louis E, Dotan I, Ghosh S, et al. Optimising the inflammatory bowel disease unit to improve quality of care: expert recommendations. *J Crohns Colitis* 2015; 9: 685–691.

101. Kapasi R, Glatter J, Lamb CA, et al. Consensus standards of healthcare for adults and children with inflammatory bowel disease in the UK. *Frontline Gastroenterol* 2020; 11: 178–187.

102. Bennett JL, Ha CY, Efron JE, et al. Optimizing perioperative Crohn's disease management: role of coordinated medical and surgical care. *World J Gastroenterol* 2015; 21: 1182–1188.

103. Schraut WH. The surgical management of Crohn's disease. *Gastroenterol Clin North Am* 2002; 31: 255–263.

104. Samaan MA, Arkir Z, Ahmad T, et al. Wide variation in the use and understanding of therapeutic drug monitoring for anti-TNF agents in inflammatory bowel disease: an inexact science? *Expert Opin Biol Ther* 2018; 18: 1271–1279.