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Disease monitoring strategies in inflammatory bowel diseases: What do we mean by “tight control”?

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Abstract

In recent years, there has been a critical change in treatment paradigms in inflammatory bowel diseases (IBD) triggered by the arrival of new effective treatments aiming to prevent disease progression, bowel damage and disability. The insufficiency of symptomatic disease control and the well-known discordance between symptoms and objective measures of disease activity lead to the need of reviewing conventional treatment algorithms and developing new concepts of optimal therapeutic strategy. The treat-to-target strategies, defined by the selecting therapeutic targets in inflammatory bowel disease consensus recommendation, move away from only symptomatic disease control and support targeting composite therapeutic endpoints (clinical and endoscopic remission) and timely assessment. Emerging data suggest that early therapy using a treat-to-target approach and an algorithmic therapy escalation using regular disease monitoring by clinical and biochemical markers (fecal calprotectin and C-reactive protein) leads to improved outcomes. This review aims to present the emerging strategies and supporting evidence in the current therapeutic paradigm of IBD including the concepts of “early intervention”, “treat-to-target” and “tight control” strategies. We also discuss the real-world experience and applicability of these new strategies and give an overview on the future perspectives and areas in need of further research and potential improvement regarding treatment targets and (“tight”) disease monitoring strategies.

Key words: Crohn’s disease; Ulcerative colitis; Treat-to-target; Tight control; Monitoring; Biomarker

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Core tip: Inflammatory bowel diseases are chronic, progressive, immune-mediated disorders leading to disability and cumulative intestinal damage. There has been a major change in treatment paradigms favouring an early introduction of highly effective therapies, applying a treat-to-target approach to target composite clinical and endoscopic therapeutic endpoints and using close monitoring of objective markers of inflammation (with clinical, endoscopic and biomarker assessment) to direct therapeutic decisions until these goals are reached. Although several data support the benefit of ‘treat-to-target’ and “tight control” strategies so far, these approaches require further validation assessing long-term outcomes and more precise definition of therapeutic targets (for both endoscopic and biomarker monitoring).

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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic immune-mediated inflammatory disorders that primarily affect the gastrointestinal tract and if uncontrolled, lead to disabling conditions that impact severely on the patient’s physical health and quality of life. The incidence and prevalence of IBD is increasing worldwide, putting significant burden on both individuals and the health care system^[1]. The past two decades have brought substantial advances in the pharmacological management of IBD by the introduction of immunosuppressive agents, biologics and lately small molecules. Numerous new drugs with different mechanisms of action have emerged, however determining the specific role of each drug in the therapeutic armamentarium of IBD has become challenging. In addition to the burst of novel therapeutic options, probably the second most important result of the past years is the observation that most therapeutic approaches driven only by symptomatic control of disease activity probably failed to change the natural course of the disease^[2-3].

The availability of new, effective therapies with biologics and the insufficiency of symptomatic disease control inherently lead to the need of reviewing conventional treatment algorithms and developing new concepts of optimal therapeutic strategy. This review aims to present the emerging trends and evidence in the current therapeutic paradigm of IBD including “early intervention”, “treating to target” and “tight control” as three pillars of a modern, individualized therapeutic approach in IBD management.

THE EVOLUTION OF TREATMENT STRATEGIES—EARLY INTERVENTION AND RISK STRATIFICATION

The treatment approach and the positioning of available therapies in the management of IBD has evolved significantly. It has now been widely acknowledged that IBD is a progressive disease and in the absence of timely and effective treatment causes cumulative structural damage and disability to the gastrointestinal tract alongside the disease course, especially in Crohn’s disease (CD)^[6-8]. The Lémann score is the first disability index for CD providing comprehensive assessment of structural bowel damage (strictures, abscesses, fistulas, and surgical requirements)^[7]. In ulcerative colitis (UC), there is less evidence whether ongoing inflammation necessarily leads to permanent bowel damage, however data suggests that UC also present a progressive nature in about one-fifth of patients (proctitis or left-sided colitis progressing to extensive colitis over time)^[3,9]. This recognition led to the revision of conventional “step-up” treatment approaches based on the idea that the introduction of more efficacious therapies early in the disease course can potentially modify the disease trajectory.

TOP-DOWN^[10] was the first trial to assess and compare different treatment algorithms in IBD. In this landmark study, treatment-naïve CD patients were randomly assigned to “top-down” strategy [start with a combination of biological

therapy and immunosuppressant-early combined immunosuppression (ECI)] compared with the standard “step-up” management (start with steroids and step up to immunosuppressant and biologics if necessary). Authors found that ECI was more effective than conventional management for achieving corticosteroid-free remission at week 52 (61.5 *vs* 42.2%; $P = 0.0278$). A subsequent trial proving the superiority of combined immunosuppression in biologic naïve CD patients was the SONIC^[11] trial. Results showed a clear benefit for ECI in terms of corticosteroid-free clinical remission at week 26. The REACT^[12] study was designed to validate the efficacy, safety and generalizability of the top-down algorithm-based therapy in community GI practices. In this study, 1982 patients with CD were randomized to receive either ECI or conventional “step-up” therapy. The composite endpoint of hospitalization, surgery and serious disease related complications was lower in patients treated with ECI strategy at 24 mo (27.7 and 35.1%, $P < 0.001$). However, the primary outcome, the proportion of patients in corticosteroid-free remission at 12 mo, was not superior (66% *vs* 61.9%; $P = 0.52$). A notable limitation to the REACT study is that although the trial is supposed to investigate the effects of “early” introduction of combined immunosuppression, a large proportion of patients had longstanding disease or prior respective surgery, and had been treated with biologics and/or immunosuppressants. The very recent CALM^[13] trial also verified the benefits of early introduction and quick escalation of immunosuppressive and biologic therapies when meeting treatment failure criteria (either clinical or biomarker). Despite certain limitations and methodological differences, the above results suggest that highly effective therapy initiated early in the course can potentially lead to better outcomes without a significant increase in drug-related risk (concept of “window of opportunity”).

It is important to recognize that a significant proportion of IBD patients have mild disease course. Population-based data suggests that 40% of patients with CD have a clinically indolent disease, and approximately half of the patients with CD will present non-complicated (B1) disease behavior 10 years after diagnosis^[8]. In both CD and UC, potentially indolent disease must be distinguished from severe disease, assuring the opportunity of early intensive therapy for the latter one, while those with indolent disease might benefit from a slower escalation of therapeutic steps, avoiding potential overtreatment. With the introduction of multiple new therapies, the identification of populations with high risk of severe disease course gained a growing interest. Predictive factors have been identified in population-based cohorts for CD, including younger age at disease onset, smoking, extensive small bowel disease, perianal disease, deep ulceration on endoscopy, prior surgery, corticosteroid use at diagnosis, and extra-intestinal manifestations^[14,15]. In the case of UC, patients with pancolitis, deep ulcers on endoscopy and non-smoking status are at higher risk for colectomy^[16]. Prediction models for assessing the probability of advanced disease 5 and 10 years after diagnosis have been developed in both CD and UC, however external validation of these prediction tools are still warranted^[16-18].

THE CONCEPT OF TREAT-TO-TARGET

The concept of “treat-to-target” has been studied and applied thoroughly in chronic diseases, such as diabetes or rheumatoid arthritis for several years and resulted in improved outcomes. For IBD patients, this concept originated from the observation that current symptom oriented therapeutic strategies failed to alter the natural progression of IBD according to the results of many population-based studies, even though immunosuppressives and biologicals have been introduced^[2-5,19-21]. This could at least partly be the results of the frequent and widely acknowledged discordance between symptoms and objective measures of disease activity, especially in CD. In a post-hoc analysis of the SONIC trial, half of the patients who were in clinical remission had evidence of residual disease activity, based on endoscopic assessment or C-reactive protein (CRP) measurement, whereas other patients with endoscopic and CRP normalization still had persistent clinical symptoms^[22]. In the case of UC, symptoms usually correlate better with endoscopic activity compared to CD, although a significant proportion of patients in clinical remission still have endoscopic activity and the normalization of stool frequency does not always follow endoscopic healing^[23]. Switching the therapeutic endpoints from clinical remission to endoscopic healing has been increasingly supported by post-hoc analyses of pivotal clinical trials. Achieving mucosal healing was shown to predict long-term steroid free remission and better outcomes in terms of surgical and hospitalization requirements^[10,24-27].

The treat-to-target concept in IBD was developed by the selecting therapeutic targets in inflammatory bowel disease (STRIDE) committee, a group of international IBD experts established by the International Organization for the Study of

Inflammatory Bowel Diseases in 2015. The treat-to-target implies the identification of a predefined goal in the context of the patient's individual needs to be achieved by the therapy, followed by regular monitoring and treatment optimization if needed, until this goal is achieved. The definition of recommended treatment targets were performed based on an evidence-based expert consensus process^[28].

In CD, the treat-to-target recommendations are composite endpoints of clinical (defined as resolution of abdominal pain and altered bowel habit) and endoscopic remission (defined as resolution of ulceration). For patients who could not be adequately assessed by ileocolonoscopy, resolution of inflammation based on cross-sectional imaging is the desired target. The primary target recommendations for UC also consist of clinical (defined as resolution of rectal bleeding and normalisation of bowel habit) and endoscopic endpoints (defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy). Biochemical targets [CRP or fecal calprotectin (FCAL)] and histopathology were not recommended as adjunctive endpoints. The use of biomarkers (CRP and FCAL) are recommended in both CD and UC for disease monitoring, and persistent failure of normalization should prompt further endoscopic or radiologic evaluation, regardless of symptoms. Imaging modalities are considered having a complementary role to endoscopy in CD, and they are not recommended for disease assessment in UC^[28].

INSTRUMENTS OF TIGHT CONTROL IN DISEASE MONITORING

At the time of the development of STRIDE, supporting evidence for target recommendations were available only from retrospective studies and post-hoc analyses of randomized clinical trials. Emerging prospective and clinical trial data with long-term outcomes of the application of the treat-to-target concept have been published, which will help further understanding of the treat-to-target approach and adjusting and optimizing the various targets in everyday clinical practice. The importance of timely assessment of disease activity has been clearly emphasized in the STRIDE creating the concept of "tight" disease control. The CALM^[13] trial was the first randomized study to show that tight disease monitoring using objective markers of inflammation and timely escalation of therapy in patients with early CD leads to better clinical and endoscopic outcomes compared to symptom-driven management alone. Objective measurement of inflammatory activity requires invasive and costly procedures, such as ileocolonoscopy or cross-sectional imaging. Levels of CRP and FCAL are among the most widely investigated non-invasive markers of inflammation in IBD. In recent years, the most significant adjustment to the STRIDE recommendations is the increasing role of biomarkers (CRP and FCAL) in treatment decisions based on the supporting results of the CALM trial. In the following sections we aim to give a detailed description and review of current evidence on each therapeutic target and their role in a "tight control" disease management (see [Table 1](#)).

Clinical targets

Although resolution of symptoms alone is not a sufficient therapeutic endpoint, it is still necessary to properly monitor and treat symptoms of the disease. Multiple clinical scoring systems have been developed in clinical practice; the Crohn's Disease Activity Index (CDAI) and Harvey Bradshaw Index (HBI) being the most widely used in CD, and the partial Mayo score (pMayo) and the Simple Clinical Colitis Activity Index in UC^[29-32].

The CDAI, HBI or pMayo scores are composite clinical scores, meaning that they include laboratory features, disease characteristics or the general assessment of the physician. As the STRIDE recommendation outlined the resolution of clinical symptoms as a separate therapeutic target, it is logical to develop independent clinical measures that reliably assess symptoms coming directly from a patient. A "patient reported outcome" (PRO) is a report from the patient's perspective about the status of their symptoms and perceived response to therapy. According to the FDA guidance, creating a PRO must involve generation of items based on qualitative patient interviews and thorough testing for responsiveness and internal consistency^[33]. Although composite clinical scores such as the CDAI and HBI indices include patient-reported severity of symptoms, their development was not conducted in accordance with these stringent requirements. In the absence of a well-characterized PRO items for IBD, the STRIDE program recommends the use of a two-item interim PRO that should be resolution of abdominal pain and normalization of bowel habit for CD, and in the case of UC, resolution of rectal bleeding and normalization of bowel habit. Assessment of clinical targets should be tailored to the patient's individual needs,

Table 1 Selected studies supporting the use of clinical, biochemical, endoscopic, histological and combined targets since the publication of selecting therapeutic targets in inflammatory bowel disease consensus

Study	Study type	Treatment targets evaluated	Patient population	Compared patient groups	Outcomes
Colombel <i>et al</i> ^[13] (CALM)	Randomized clinical trial	Combined clinical and biomarker	CD- 244 patients	Incremental therapy escalation based on "tight control" with biomarker (CRP and FCAL) and clinical assessment every 12 wk <i>vs</i> "clinical management" with only clinical assessment	Outcomes at 48 wk: Mucosal healing (CDEIS < 4 and no deep ulcerations), 45.9% <i>vs</i> 30.3%; <i>P</i> = 0.010 steroid free remission, 59.8% <i>vs</i> 39.3%; <i>P</i> < 0.001 deep remission (CDAI < 150, CDEIS < 4 and no deep ulcers), 36.9% <i>vs</i> 23.0%; <i>P</i> = 0.014 biological remission (FCAL < 250 µg/g, CRP < 5 mg/L, and CDEIS < 4), 29.5% <i>vs</i> 15.6; <i>P</i> = 0.006
Ungaro <i>et al</i> ^[55] (CALM – long term extension)	Randomized clinical trial	Endoscopy	CD – 122 patients	Endoscopic remission (CDEIS < 4 and no deep ulcerations) at 1 yr <i>vs</i> NOT Deep remission (CDAI < 150, CDEIS < 4 and no deep ulcers) at 1 yr <i>vs</i> NOT	Composite of major adverse outcomes reflecting CD progression: New internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalization, or CD surgery (median 3 yr follow-up after end of CALM): aHR = 0.44, 95%CI: 0.20-0.96, <i>P</i> = 0.038 aHR = 0.25, 95%CI: 0.09-0.72, <i>P</i> = 0.01
Shah <i>et al</i> ^[38]	Meta-analysis	Endoscopy	CD – 673 patients (12 studies included)	Achieving MH at first endoscopic assessment after therapy initiation <i>vs</i> NOT	Outcomes reported at ≥ 50 wk: Clinical remission [OR] 2.80, 95%CI: 1.91-4.10 maintenance of mucosal healing [OR] 14.30, 95%CI: 5.57-36.74 resective surgery [OR] 2.22, 95%CI: 0.86-5.69
Shah <i>et al</i> ^[39]	Meta-analysis	Endoscopy	UC – 2073 patients (13 studies included)	Achieving MH at first endoscopic assessment after therapy initiation <i>vs</i> NOT	Outcomes reported at ≥ 50 wk: clinical remission [OR] 4.50, 95%CI: 2.12-9.52 avoiding colectomy [OR] 4.15, 95%CI: 2.53-6.81 maintenance of mucosal healing [OR] 8.40, 95%CI: 3.13-22.53 long-term corticosteroid-free clinical remission [OR] 9.70, 95%CI: 0.94-99.67
Park <i>et al</i> ^[70]	Meta-analysis	Histology	UC – 13 studies included	Histological remission <i>vs</i> NO histological remission at baseline Histological remission <i>vs</i> NO histological remission at baseline among patients in combined clinical and endoscopic remission	Outcomes up to 12 mo follow-up: Clinical relapse/ exacerbation [RR] 0.48, 95%CI: 0.39–0.60 Clinical relapse/ exacerbation [RR] 0.81, 95%CI: 0.70–0.94
Bryant <i>et al</i> ^[68]	Prospective	Histology	UC – 91 patients	Histological remission <i>vs</i> NO histological remission at baseline	Outcomes reported over a median 72 mo follow-up: corticosteroid use [HR] 0.42, 95%CI: 0.2–0.9; <i>P</i> = 0.02 acute severe colitis requiring hospitalization [HR] 0.21, 95%CI: 0.1–0.7; <i>P</i> = 0.02

Lasson <i>et al</i> ^[93]	Prospective, Randomized	Biomarker	UC – 91 patients	Monthly FCAL measurement: Dose-escalation of 5-ASA in patients with FCAL > 300 µg/g <i>vs</i> NO intervention	18 mo follow-up: Fewer clinical relapses observed in intervention group, 28.6% <i>vs</i> 57.1%; <i>P</i> <0.05
Zhulina <i>et al</i> ^[52]	Prospective	Biomarker	CD – 49 patients; UC – 55 patients	First clinical relapse <i>vs</i> NO relapse in patients with clinical remission at baseline	2 yr of follow-up: Doubling of faecal calprotectin level between two consecutively samples 3 mo apart predicted relapse [HR] 2.01, 95%CI: 1.53-2.65
Sollelis <i>et al</i> ^[94]	Prospective	Combined clinical and biomarker	CD – 40 patients	Clinical and biomarker remission at 12 wk (CDAI < 150 and CRP ≤ 2.9 mg/L and FCAL < 300 µg/g) <i>vs</i> NOT	Predictive power for corticosteroid-free clinical remission at 52 wk: Sensitivity = 69.2% (42.0-87.4) specificity = 100.0% (84.9-100.0) PPV = 100.0% (100.0-100.0) NPV = 87.1% (75.3-98.9)

CD: Crohn's disease; UC: Ulcerative colitis; CRP: C-reactive protein; FCAL: Fecal calprotectin; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity; 5-ASA: 5-aminosalicylic acid; RR: Relative risk; HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; aHR: Adjusted hazard ratio.

with a minimum of every 3 mo during active disease and every 6-12 mo after symptom resolution for both CD and UC^[28] (see Table 2).

Since the STRIDE recommendations, newer PRO tools, including more clinical variables (abdominal pain and urgency for UC) in accordance with FDA guidance, have been developed, however their applicability in clinical trial design or everyday clinical practice still remain to be validated^[34-36]. Various other PROs have already been used in clinical trials reporting depression, anxiety, disability and other quality of life parameters, however available data on these PROs in IBD are yet limited. The IBD disability index (IBD-DI), developed in accordance with the WHO International Classification of Functioning is a validated tool to measure disability, and shows good correlation with clinical disease activity^[37]. Future studies will assess the role of IBD-DI as a potential clinical target.

Endoscopic targets

Numerous recent studies support the STRIDE recommendation to target endoscopic healing, since several clinical trials (post-hoc analysis) and population-based studies have demonstrated that achieving mucosal healing is associated with improving outcomes, such as lower rates of hospitalizations, disease relapse, and lower surgery requirements^[24-27]. In a systematic review and meta-analysis of 12 studies, endoscopic remission (or mucosal healing) on the first post-treatment endoscopy was associated with a higher rates of long-term clinical remission [pooled odds ratio (OR) = 2.80, 95%CI: 1.91-4.10], maintenance of mucosal healing (14.30, 95%CI: 5.57-36.74), and lower risk of surgery (2.22, 95%CI: 0.86-5.69) in patients with CD^[38]. The same meta-analysis of 13 studies was performed for UC, resulting that mucosal healing on the first post-treatment endoscopy was associated with long-term (52 wk) clinical remission [OR = 4.50, 95%CI: 2.12-9.52], avoiding colectomy (4.15, 95%CI: 2.53-6.81), achieving long-term corticosteroid-free clinical remission (9.70, 95%CI: 0.94-99.67), and long-term mucosal healing (8.40, 95%CI: 3.13-22.53)^[39]. The feasibility of applying a treat-to-target approach in regard to mucosal healing was studied by Bouguen *et al*^[40]. Sixty-seven CD patients with endoscopic lesions underwent two to four subsequent endoscopies with a median follow-up of 76 wk. Factors associated with achieving mucosal healing were fewer than 26 wk between endoscopic procedures [hazard ratio (HR) = 2.21; 95%CI: 1.16-4.26; *P* = 0.016] and adjustment to medical therapy when mucosal healing was not observed (2.35; 95%CI: 1.2-4.94; *P* = 0.012), concluding that serial endoscopic procedures and treatment optimizations accordingly are feasible in clinical practice and high rates of MH can be achieved.

Although, the predictive value of early mucosal healing and the need for applying endoscopic targets as primary therapeutic endpoints is clear, the definition for optimal endoscopic targets is lacking. The STRIDE recommendations specify endoscopic targets as resolution of ulceration in CD and resolution of ulceration and friability in UC assessed at 6-9 mo and 3-6 mo after commencing therapy, respectively^[28] (Table 2). The definition of mucosal healing is however highly

Table 2 Intervals of clinical, biomarker, and endoscopic assessment in the treat-to-target and tight control framework

	Active disease/at flare	Clinical remission
Crohn's disease		
Clinical evaluation (PRO, CDAI, HBI indices)	3 mo [STRIDE and CALM protocol] ^[28,13]	6-12 mo [STRIDE] ^[28] 3 mo [CALM protocol] ^[13]
Endoscopic evaluation	6-9 mo after therapy initiation [STRIDE] ^[28]	Based on screening recommendations in deep remission Prompted by clinical symptoms or (consecutive) biomarker positivity – FCAL ^[52,53]
Biomarker evaluation (CRP and FCAL)	3 mo (FCAL + CRP) [CALM protocol] ^[13,94] Approximately 12-14 wk after therapy initiation (CRP) ^[95,96] Approximately 14 wk after therapy initiation (FCAL) ^[94,97,98]	3 mo (FCAL + CRP) [CALM protocol] ^[13] (2)-3 mo (FCAL) ^[52,53] 3 mo (CRP) ^[99]
Ulcerative colitis		
Clinical evaluation (PRO, CDAI, HBI indices)	3 mo [STRIDE] ^[28]	6-12 mo [STRIDE] ^[28]
Endoscopic evaluation	3-6 mo after therapy initiation [STRIDE] ^[28]	Based on screening recommendations in deep remission Prompted by clinical symptoms or (consecutive) biomarker positivity – FCAL ^[52,53]
Biomarker evaluation (CRP and FCAL)	Approximately 10 wk after therapy initiation (FCAL) ^[100]	(2)-3 mo ^[51-53,101]

¹Using C-reactive protein alone has only moderate predictive value in identifying relapse in patients with clinical remission. PRO: Patient reported outcome; CDAI: Crohn's Disease Activity Index; HBI: Harvey Bradshaw Index; CRP: C-reactive protein; FCAL: Fecal calprotectin; STRIDE: Selecting therapeutic targets in inflammatory bowel disease.

heterogenous, especially in CD. The most commonly accepted definition of endoscopic healing is the disappearance of all ulcerative lesions, however this definition does not allow for the interpretation of partial resolution of mucosal inflammation. A different solution would be the use of reproducible endoscopic activity scores capable of depicting precise degree of endoscopic activity and subsequent changes. Widely used endoscopic scores in CD are the Crohn's disease Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score for Crohn's disease (SES-CD), and Rutgeerts' score for post-surgical evaluation of endoscopic recurrence. In UC, the endoscopic Mayo score and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) are most frequently used. However, the proper definition of "optimal" or "targeted" degree of endoscopic healing is lacking.

A post-hoc analysis of the SCONIC trial tried to identify an optimal definition for endoscopic healing/remission that would predict long term outcomes in CD. Mucosal healing (resolution of ulcers) and endoscopic response (defined as a decrease from baseline SES-CD or CDEIS by at least 50%) at week 26 showed the best performance in identifying those most likely to be in corticosteroid-free clinical remission at week 50, however AUC values were fairly modest in either case, moreover a higher decrease from baseline SES-CD or CDEIS scores did not show better predictive performance^[41]. This further strengthens the fact that the desired degree of endoscopic healing to reach superior long-term outcomes or the absence of endoscopic improvement which should prompt therapy change is largely unknown. The same problem applies for clinical trial design where the absence of validated definitions of endoscopic healing leads to the arbitrary choice of endoscopic endpoints by investigators. Recently, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) reviewed endoscopic scoring systems and achieved consensus on definitions of endoscopic remission and response in CD. Expert investigators chose a > 50% decrease in SES-CD or CDIES for the definition of endoscopic response, and an SES-CD 0-2 for the definition of endoscopic remission^[42]. Of note, these recommendations are yet to be subjected to thorough validation and prospective testing before widely incorporated into clinical trial endpoints or everyday clinical practice.

Although endoscopic healing is a critical target in UC, the scoring systems and endoscopic criteria of healing also warrant revision. Generally, a Mayo 0 or 1 endoscopic score is considered to be endoscopic remission, however new data show that a score of 0 is associated with lower risk of clinical relapse compared with a score of 1^[43,44]. Updates in the endoscopic Mayo score incorporating disease extent correlate well with clinical and endoscopic outcomes and may improve the applicability and accuracy of the most widely used scoring system^[45]. The UCEIS is also accurate and responsive, and takes ulcer size and depth in consideration, parameters that are not captured by the endoscopic Mayo score, however the assessment of friability is excluded from the UCEIS^[46]. Recently, the IOIBD suggested the use of UCEIS of 0 as the definition of endoscopic remission and a decrease in Mayo endoscopic score ≥ 1

grade or a decrease in UCEIS ≥ 2 points for the definition of endoscopic response in UC^[47].

Biochemical targets

The most broadly used and thoroughly studied biomarkers are the serum CRP and FCAL. In general, elevated CRP levels in CD are associated with clinical disease activity and endoscopic inflammation^[48]. Compelling results show that early normalization of CRP is associated with therapeutic response in CD and in patients having an elevated CRP concentration at baseline, changes in CRP may provide useful information in monitoring treatment response. However, CRP is not a specific marker of intestinal inflammation with an overall specificity of 0.49 (95%CI: 0.72–0.98) in CD, moreover, approximately 20% of patients do not present with an elevated CRP during disease flare^[49]. Much less data support the applicability of CRP measurements in UC as many patients with UC do not have elevated CRP levels. However, serial measurements may be useful for assessment of treatment response in patients with severe colitis.

FCAL is a highly sensitive marker of endoscopic disease activity in both UC and CD^[49]. However, identifying the optimal FCAL concentration cut-off values best predictive of disease activity is challenging. D'Haens *et al*^[50] suggested a fecal calprotectin cut-off value of 250 $\mu\text{g/g}$, as levels above this concentration predicted large ulcers in CD (sensitivity 60%, specificity 80%) and active mucosal disease (Mayo score > 0) in UC (sensitivity 71%, specificity 100%). A recent study also demonstrated that during the regular monitoring of FCP levels, two consecutive FCAL measurements of $> 300 \mu\text{g/g}$ with 1-mo interval were identified as the best predictor of disease flare (61.5% sensitivity and 100% specificity)^[51]. Furthermore, two recent studies showed that patients had significantly higher FCAL levels as soon as 3 mo before disease flare^[51,52]. Zhulina *et al*^[52] reported that doubling of faecal calprotectin level between two consecutively collected samples 3 mo apart was associated with a 101% increased risk of relapse (HR = 2.01; 95%CI: 1.53–2.65; $P < 0.001$). A systematic analysis of six studies has shown that increased levels of FCAL on at least two consecutive measurements were associated with a higher risk of relapse within 2–3 mo in asymptomatic patients^[53]. In predicting relapse after surgery, evidence suggests that FCAL may be best utilized as a monitoring strategy for postoperative recurrence, with values $< 100 \mu\text{g/mg}$ strongly suggesting no recurrent disease^[54] (see Table 2).

Biochemical targets (CRP or FCAL) were not recommended by STRIDE as primary treat-to-target endpoints due to lack of sufficient evidence in support of their use at the time the guidance. However, their use is recommended in both CD and UC as adjunctive measure to monitor disease activity^[28]. The use of biomarkers for disease monitoring has the advantage of being non-invasive and relatively inexpensive. The above results suggest that after identifying the appropriate cut-off levels, the combined measurement of these biomarkers (FCAL and CRP) could very much help disease monitoring and decision making about the optimal timing of endoscopy. Significant progress has been made since the STRIDE recommendations in this regard.

The most compelling evidence for the tailored use of biomarkers in tight disease monitoring derives from the CALM^[13] study, seeking whether it is appropriate to intensify therapy in patients based on close monitoring of inflammatory biomarkers (CRP and/or FCAL). The CALM study is the first randomized trial to demonstrate that in patients with early CD, therapy based on biochemical targets in addition to clinical targets (tight control arm) is associated with higher endoscopic remission at 1 year compared with therapy based on clinical targets alone (clinical management arm). Treatment in both arms was escalated in a stepwise manner from no treatment to adalimumab induction, followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. Evaluations were performed at 12, 24, and 36 wk and escalation was based on meeting one of the following failure criteria; tight control group: faecal calprotectin $\geq 250 \mu\text{g/g}$, CRP $\geq 5\text{mg/L}$, CDAI ≥ 150 or prednisone use in the previous week; clinical management group: CDAI decrease of < 100 points compared with baseline or CDAI ≥ 200 , or prednisone use in the previous week. For the tight control arm, even if patients were symptomatically well, treatment was escalated if biomarkers were raised. The primary outcome at 48 wk after randomisation was mucosal healing (CDEIS < 4 and no deep ulcerations). A significantly higher proportion of patients achieved the primary endpoint (46% *vs* 30%; adjusted risk difference 16.1%, 95%CI: 3.9–28.3; $P = 0.010$) when applying a tight control strategy, compared to symptom-driven clinical management. In addition, fewer CD-related hospitalizations occurred in the tight control arm (13.2 *vs* 28.0 events/100 patient-years; $P = 0.021$). Subsequent follow-up data of the CALM study on 122 patients for 3 additional years revealed that endoscopic remission [adjusted hazard ratio = 0.44, 95%CI: 0.20–0.96] and combined endoscopic and clinical (deep) remission (0.25, 95%CI: 0.09–0.72) at 1 year were

associated with lower risk of adverse events such as new internal fistula/abscess, stricture, perianal fistula/abscess, hospitalization, or surgery in long-term follow-up^[55]. These data further strengthen the STRIDE recommendations for targeting combined endoscopic and clinical remission and adds the importance of the timely assessment and aiming for normalization of biochemical markers.

Therapeutic drug monitoring (TDM) is an integral component of tight disease monitoring in IBD. Numerous studies have shown that optimal levels of anti-TNF agents are associated with clinical and endoscopic remission, and conversely, low drug levels are associated with reduced clinical efficacy, suboptimal control of inflammation, and higher risk of disease flares^[56-58]. The most evidence support the role of drug Trough Level (TL) and anti-drug antibody (ADA) evaluations ideally in patients losing response to biologic therapy– *i.e.*, reactive TDM in the case of suspected loss of response (LOR)^[59-61]. The use of reactive TDM is based on a widely known algorithmic approach, originally developed to assess treatment failure (LOR) in patients treated with anti-TNF agents (see Table 3). There are currently insufficient data to determine the exact role of TDM in other newer biologics, such as vedolizumab or ustekinumab.

Results of clinical trials investigating the benefit of proactive/routine drug monitoring have been however somewhat disappointing. In the TAXIT (Trough Level Adapted Infliximab Treatment) trial, no difference in the primary outcomes (clinical remission at 1 year) was observed between patients randomly assigned to a drug-monitoring group in which infliximab dosing was continuously adjusted, (drug levels within 3–7 µg/mL), or to a conventional therapy group, with infliximab dosing based on clinical symptoms alone (69% *vs* 66%; $P = 0.686$)^[62]. The TAILORIX (Tailored treatment with infliximab for active CD) trial also studied CD patients receiving infliximab and subsequent dose-escalation guided by infliximab levels, biomarkers and clinical symptoms *vs* clinical symptoms alone. No significant difference was observed between the patient groups for the primary outcome of steroid-free clinical remission at 22 and 54 wk^[63-65]. Although other single cohort or retrospective studies show potential benefits of proactive TDM^[66], based on the above trials it is questionable whether routine proactive monitoring of aTNF agents lead to improving outcomes, or TDM measurements can be reserved optimally for assessment of therapeutic failure. Observational studies also show that measuring drug and anti-drug antibody levels can guide decisions for anti-TNF withdrawal or restart after a drug holiday^[67]. Further reviewing the available evidence on TDM is beyond the scope of this article.

Histologic targets

Histologic remission, which means resolution of inflammation on microscopical/histological examination of the colonic mucosa, was not recommended as a target by the STRIDE recommendation due to lack of sufficient evidence. Lately, histological assessment in UC has an emerging role in clinical trials. Recent studies consistently suggest that achieving histologic remission may demonstrate better prognostic value in long-term outcomes (relapse-free survival, corticosteroid use, and hospitalization) than endoscopy^[68,69]. In a meta-analysis of 15 studies, the risk of UC exacerbation was lower with histologic remission compared with patients with histological activity but in endoscopic and clinical remission [pooled OR = 0.81, 95% CI: 0.70–0.94]^[70]. Several histologic scoring systems are available in UC, the Nancy index and the Robarts Histopathology Index (RHI) being properly validated and showing good correlation with endoscopic disease activity and biomarkers, however optimal endpoints in histologic healing are yet to be determined^[71]. In the case of CD, there are very few data to support histologic remission as a treatment target. The lack of a validated histologic scoring systems to identify remission and the risk of sampling error due to the manifestation of CD (skip-lesions) limit the applicability of histologic assessment.

Imaging targets

Several study demonstrated that cross-sectional imaging have superior diagnostic accuracy compared to ileocolonoscopy in extensive ileal, stricturing or penetrating CD, and have a higher impact on therapeutic decisions in appropriate patients^[72]. The STRIDE consensus recommended resolution of lesions in cross-sectional imaging as not a universal target, although imaging modalities should have a complementary role in patients with CD who cannot be adequately assessed by colonoscopy. Further data in CD patients using imaging modalities to target resolution of inflammation have been reported since the publication of STRIDE. In a retrospective analysis, complete resolution of small bowel lesions on CTE or MRE was associated with a decrease in hospitalization [(HR), 0.28, 95% CI: 0.15–0.50] and surgery (0.34, 95% CI: 0.18–0.63) over a median of 9 years observed period^[73]. Patients with transmural

Table 3 Therapeutic drug monitoring-based algorithm for handling patients with treatment failure on biologic therapy^[59-61]

	Detectable anti-drug antibodies	Undetectable anti-drug antibodies
Sub-therapeutic anti-TNF drug levels	Change to different TNF-inhibitor.	Intensify the treatment regimen of the currently used TNF-inhibitor.
Therapeutic anti-TNF drug levels	(Repeat assessments of anti-TNF drug and anti-drug antibodies over time) Switch to another biological agent with a different mechanism of action.	Switch to another biological agent with a different mechanism of action.

TNF: Tumor necrosis factor.

healing on MRE presented lower rates of therapy escalation, hospital admission and surgery at 1 year in a prospective cohort^[74]. In a retrospective study, fast-track MRI examinations coupled with clinical and biomarker activity assessment had a significant impact on patient management, leading to better patient stratification and earlier optimization of the therapy (medical or surgical)^[75]. Abdominal ultrasound (US) is a safe and inexpensive diagnostic modality, and shows comparable overall diagnostic performance to MRI and CT modalities in ileal CD^[72]. Recently, several US indices have been developed for assessing disease activity, however further validation of these tools and their impact in disease monitoring need more research^[76].

Cross-sectional imaging modalities are not recommended by the STRIDE in the evaluation of UC, considering that it is primarily a mucosal disease. However, the MaRIA MRI index or diffusion-weighted MRI modalities studied mainly in patients with CD, have high sensitivity in detecting mucosal lesions, thus could have potential applicability in UC^[77]. The lack of invasiveness and radiation exposure makes MRI an attractive diagnostic tool, although further investigation is definitely warranted however to demonstrate long-term outcomes in MRI guided therapeutic strategies.

TREATMENT DE-ESCALATION

As a result of the changing treatment paradigms, there has been an exponential increase in the exposure to immunosuppressive and biologic agents. Several long-term trials have shown that discontinuation of therapy is associated with high relapse rates, suggesting that cessation of biologics can be considered only in selected patients. It is important to recognize that tight control management strategies could also help identifying those patients through proper disease monitoring strategies and not only promote therapy escalation but de-escalation as well. The STORI (infliximab discontinuation in CD patients in stable Remission on combined therapy with Immunosuppressors) trial showed that the relapse rate within a 1 year of discontinuation was approximately 50%, however, patients having ≤ 2 risk factors, including male gender, elevated leukocytes, an elevated CRP level, elevated FC level, and decreased hemoglobin showed only a 15% risk of relapse^[78]. Safety signals were not different between patient groups in the CALM^[13] study despite a higher exposure to combined immunosuppression in the tight control arm, nevertheless, safety concerns regarding combined immunosuppression and the huge increase in drug related costs makes it necessary to develop appropriate de-escalation strategies for selected patients, and determine the exact role of biomarkers and endoscopy in this area as well.

REAL-WORD EXPERIENCE WITH TREAT-TO-TARGET STRATEGIES

Although the treat-to-target and tight control strategies seem to achieve improved long-term outcomes in CD and UC, certain factors can limit the applicability and acceptance of these new paradigms in clinical practice. Although there are reports of these new strategies to be properly translated in clinical practice in several IBD centers, some studies propose significant gaps in the implementation of treat-to-target strategies^[79,80]. The overall increase in doctor-patient visits, laboratory testing, and endoscopies could be “burdensome” for both patients and physicians and could potentially slow the uptake of treat-to-target strategies, especially in community gastroenterology services. In contrast to the STRIDE recommendations, which advocate for endoscopic evaluation after 3 mo of therapy start in active UC,

endoscopy was performed in only 47% of such patients within 3 mo, and in 68% within 6 mo in a recent Australian multicenter study of IBD outpatient services^[80]. In the same study, a clinician survey was performed showing that 80% of respondents had heard of the “treat-to-target” concept, 61% were familiar with the recommendations, but only 64% considered it relevant to local clinical practice.

It is important for individual IBD centers to assess and measure local therapeutic strategies and processes, and evaluate whether they are in concordance with current expert recommendations and consensus Quality of Care standards^[81,82]. A study by Reinglas *et al*^[83] is one of the few reporting a detailed assessment of patient evaluation strategies, disease monitoring, treatment decisions, disease-related outcomes from a tertiary care IBD center in Canada. Results confirmed the application of objective patient re-evaluation and monitoring (ileocolonoscopy or colonoscopy was performed in 79% of all IBD patients within the past 2 years from a chosen time point), timely access to diagnostic procedures and accelerated treatment pathways. Another example for the application of tight control strategies is from Hungary, where a harmonized monitoring strategy is mandatory with serial clinical (CDAI and pMayo scores) and laboratory (CBC and CRP) assessments reported every 3 mo as requested by the Hungarian National Health Fund for patients receiving biologic therapies^[84].

A properly working platform for rapid patient access (in case of flare or other IBD related emergency situations) is equally important in the framework of “tight control” management. A special emphasis on providing rapid patient access could potentially help avoiding undesirable outcomes such as steroid dependency, frequent Emergency Department (ED) visits or emergency hospitalizations/surgeries. Several data show that inadequate ‘patient access’ to treating physician or healthcare services is frequently a source of dissatisfaction among patients^[85]. Our group performed a detailed analysis of patient access, diagnostic procedures, resource utilization, and outcome parameters after the implementation of a new Rapid Access Clinic service at the McGill University Health Centre tertiary care IBD center. Patients presenting with flare had a fast-track clinical and biomarker evaluation (CRP and FCAL measured in 91% and 73%) within a median of 2 d. Patient evaluations by an IBD specialist instead of the ED services led to a more optimal resource utilization (fewer cross-sectional imaging and fewer hospitalizations) in the majority of cases^[86].

Targeting MH as treatment endpoint and the tight control strategies may result in a potential increase in healthcare costs because of the more frequent use of diagnostic procedures and services and more importantly the increased rate of therapy escalations (dose intensification of biologics). Whether these additional costs could be balanced by the reduction of other healthcare expenditures associated with the long-term remission could also have major influence on the real-world application of the treat-to-target strategies. A decision analysis model performed by Ananthakrishnan *et al*^[87] using existing clinical trial data demonstrated that targeting MH was more effective at a 2 year endpoint (QALY 0.71) compared to convention clinical management strategies (QALY 0.69) with an incremental cost-effectiveness ratio (ICER) of \$ 47,278/QALY gained. A similar cost-effectiveness analysis of the CALM trial was also performed. At 48 wk, the tight control arm produced a total of £ 13296 in direct medical costs and a QALY of 0.684, while the same results were £ 12627 and 0.652 for the clinical management arm. The difference in costs (£ 669) divided by the difference in QALY (0.032) produced an ICER of £ 20913 per QALY gained which is within the acceptable range that is considered cost-effective (\$ 50–100000/QALY gained)^[88,89]. Further investigations are however needed to determine the cost-effectiveness of treat-to-target strategies in reducing disease progression, taking into account proper de-escalation strategies as well.

FUTURE PERSPECTIVES AND UNANSWERED QUESTIONS—EXPERT OPINION

In recent years, there has been a critical change in the treatment paradigms with the arrival of biologic agents. Many studies showed that the introduction of highly effective treatments in selected patients early in the disease course is crucial in achieving deep remission and avoiding disease complications. An important limitation to the landmark clinical trials evaluating the early use of biologics and immunosuppressives is that they only measured clinical outcomes as primary endpoints and endoscopic data are usually available in a subgroup of patients, except for the CALM study. In this regard, the CURE^[90] study is currently underway and is evaluating the impact of early adalimumab therapy on the disease course in CD, including mucosal healing. Personalization of the therapeutic strategy by proper early patient stratification have an increasingly important role in selecting patients who

benefit from early aggressive therapy.

The other pillar of achieving sustained deep remission is a stringent patient follow-up and timely re-evaluation. The current focus on objective parameters as treatment targets is an important step towards that direction, as proposed by the STRIDE guidance. Since the STRIDE recommendations have been published, an increasing amount of clinical data emerged on the use of various targets and subsequent long-term outcomes, thus the re-evaluation of the recommendations and targets (*e.g.*, the role of biomarkers) is warranted.

Recent long-term follow-up data of the CALM study show that endoscopic and deep remission at 1 year prevents disease progression in early CD^[55], however further clinical trials are needed to demonstrate the long-term superiority of treating to endoscopic remission. The REACT2 trial (Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy trial) assesses the exact role of endoscopy in the tight control concept by comparing an enhanced treat-to-target strategy featuring early use and rapid escalation of combined antimetabolite/adalimumab therapy based on timely endoscopic evaluations with a traditional step-care algorithm with symptom driven treatment escalation (ClinicalTrials.gov: NCT01698307)^[91]. In addition, a unified definition of endoscopic response/remission tailored to the everyday clinical practice is missing, especially in CD.

The evidence is clearly increasing on the role of biomarkers, supported by the positive results of the CALM study. Biomarkers emerge as treatment targets as they can guide treatment escalations, leading to superior endoscopic and clinical outcomes, which is the foundation of the tight control concept. However, more evidence is needed to determine the optimal role and cut-offs of biomarkers in monitoring disease control. Using directly the "therapeutic failure" from the CALM study solely based on biomarker positivity to prompt therapy escalation in certain cases would potentially be overly stringent in everyday clinical practice, leading to frequent overtreatment. Long term cost-efficacy has to be established as well. Further data is needed to evaluate the role of different biomarkers, especially used as composite (biomarker and endoscopic) "treatment failure" criteria.

Other elements of the treat-to-target and tight control strategies, such as the adequate intervals of patient monitoring also need clarification. Although the STRIDE specifies recommendations for timing of clinical and endoscopic evaluations, data on optimal biomarker follow-up intervals are partly conflictive. Moreover, patients in different clinical scenarios—active disease, clinical remission or at relapse, mild(er) or complex complicated disease—may require different disease monitoring strategy and intervals. Biomarker evaluations were performed every 12 wk in the CALM, and other studies reported that FCAL may predict clinical flare as soon as approximately 3 mo before symptoms occur. These data may suggest an optimal interval of approximately 3 mo for biomarker monitoring in patients with clinically controlled disease, however detailed recommendations for patient monitoring intervals—including clinical, biochemical and endoscopic evaluation as well— is urgently needed (see Table 2).

Although there has been a significant increase and earlier exposure to immunosuppressive and biologic agents in IBD recently, population-based data on long-term outcomes show somewhat controversial results and prompt caution when translating clinical trial results into clinical practice. The Epi-IBD^[5] cohort is a prospective population-based inception cohort of unselected CD patients from 29 European centres. Although significant geographic differences were observed in medication timing and exposures (in Western Europe 33% of patients received biological therapy and 66% immunomodulators; in Eastern Europe 14% and 54%, respectively, $P < 0.01$), the course of disease—including rates of patients undergoing surgery, developing stricturing or penetrating disease phenotype or being hospitalized— did not differ between in Western and Eastern Europe. Similar results are being reported from two very recent administrative database analyses from Canada. Data from Murthy *et al*^[92] showed that the introduction of anti-TNF therapy failed to modify the trend of IBD-related hospitalizations and surgeries in both CD and UC between 1995 and 2012. This suggests that disease monitoring in real life practice is suboptimal and in the future, using new, algorithm-based therapeutic strategies as standard of care may translate into improved outcomes as observed in pivotal clinical trials^[12,28].

CONCLUSION

Data favoring the treat-to-target strategies and tight patient control still continue to accumulate and results from ongoing trials will further clarify its long-term

implications. Early and effective treatment with optimal patient stratification and monitoring using treat-to-target and tight control concepts is emerging as superior therapeutic strategy. The use of biologic agents should be optimized with timely monitoring, appropriate treatment escalation and de-escalation strategies are both warranted in selected patients. Finally, improving patient-physician communication and patient access to IBD specific healthcare services to receive proper evaluation in urgent IBD related situations is vital in the framework of tight control management. These approaches however require further validation with more precise definition of therapeutic targets (endoscopic, biomarker) in prospective studies of newly diagnosed patients with assessment of long-term outcomes.

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