**Name of Journal:** *World Journal of Gastrointestinal Pharmacology and Therapeutics*

**Manuscript NO:** 91591

**Manuscript Type:** EDITORIAL

**Treatment endpoints in ulcerative colitis: Does one size fit all?**

Mitrev N *et al*. Treatment endpoints in ulcerative colitis

Nikola Mitrev, Viraj Kariyawasam

**Nikola Mitrev, Viraj Kariyawasam,** Department of Gastroenterology, Blacktown Hospital, Blacktown 2148, NSW, Australia

**Nikola Mitrev, Viraj Kariyawasam,** Blacktown/Mt Druitt Clinical School, University of Western Sydney, Blacktown 2148, NSW, Australia

**Nikola Mitrev,** Department of Gastroenterology, Wollongong Hospital, Loftus St, Wollongong 2500, NSW, Australia

**Author contributions:** Mitrev N contributed to research and initial write up of the manuscript, Kariyawasam V contributed to research and editing of the manuscript.

**Corresponding author: Nikola Mitrev, BSc, FRACP, MBBS, MPhil, Doctor,** Department of Gastroenterology, Blacktown Hospital, 18 Blacktown Road, Blacktown 2148, NSW, Australia. nikola.m@hotmail.com

**Received:** December 31, 2023

**Revised:** February 28, 2024

**Accepted:** April 10, 2024

**Published online:** May 5, 2024

**Abstract**

A treat-to-target strategy in inflammatory bowel disease (IBD) involves treatment intensification in order to achieve a pre-determined endpoint. Such uniform and tight disease control has been demonstrated to improve clinical outcomes compared to treatment driven by a clinician’s subjective assessment of symptoms. However, choice of treatment endpoints remains a challenge in management of IBD *via* a treat-to-target strategy. The treatment endpoints for ulcerative colitis (UC), recommended by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus have changed somewhat over time. The latest STRIDE-II consensus advises immediate (clinical response), intermediate (clinical remission and biochemical normalisation) and long-term treatment (endoscopic healing, absence of disability and normalisation of health-related quality of life, as well as normal growth in children) endpoints in UC. However, achieving deeper levels of remission, such as histologic normalisation or healing of the gut barrier function, may further improve outcomes among UC patients. Generally, all medical therapy should seek to improve short- and long-term mortality and morbidity. Hence treatment endpoints should be chosen based on their ability to predict for improvement in short- and long-term mortality and morbidity. Potential benefits of treatment intensification need to be weighed against the potential harms within an individual patient. In addition, changing therapy that has achieved partial response may lead to worse outcomes, with failure to recapture response on treatment reversion. Patients may also place different emphasis on certain potential benefits and harms of various treatments than clinicians, or may have strong opinions re certain therapies. Potential benefits and harms of therapies, incremental benefits of achieving deeper levels of remission, as well as uncertainties of the same, need to be discussed with individual patients, and a treatment endpoint agreed upon with the clinician. Future research should focus on quantifying the incremental benefits and risks of achieving deeper levels of remission, such that clinicians and patients can make an informed decision about appropriate treatment end-point on an individual basis.

**Key Words:** Ulcerative colitis; Treatment endpoints; Endoscopic remission; Histologic remission; Biomarkers; Gut barrier healing

**©The** **Author(s) 2024.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation**: Mitrev N, Kariyawasam V. Treatment endpoints in ulcerative colitis: Does one size fit all? *World J Gastrointest Pharmacol Ther* 2024; 15(2): 91591

**URL**: https://www.wjgnet.com/2150-5349/full/v15/i2/91591.htm

**DOI**: https://dx.doi.org/10.4292/wjgpt.v15.i2.91591

**Core Tip:** Recently, more stringent treatment endpoints have emerged such as histologic remission and functional gut barrier healing, which may be better predictors of clinically important outcomes compared to mucosal healing. However, pursuing deeper levels of remission in ulcerative colitis patients can have risks. Treatment endpoints in ulcerative colitis should be set with two thresholds, minimum and ideal endpoints to be achieved. Endpoints also need to be appropriate for both the follow up timeframe and the treatment selected. Individual patient circumstances need to be taken into account in selecting endpoints, as at times relaxed treatment endpoints are appropriate.

**INTRODUCTION**

Treatment of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD), relies on medications and at times surgery to induce and maintain remission. Treat-to-target treatment approach was first utilised by rheumatologists, with subsequent adoption into IBD management[1]. This approach assesses treatment adequacy against a predetermined treatment endpoint. If the treatment endpoint is not achieved after an appropriate follow up period from treatment initiation, then treatment is modified. These steps are repeated till the treatment endpoint is achieved. Having such a strategy to treat to a defined and uniform endpoint, as oppose to a clinician’s subjective assessment of disease activity, has been shown to achieve early and tight control of disease activity in CD[2]. Studies also indicate that in UC, inflammation leads to progressive bowel damage[3]. Tight disease control *via* a treat-to-target approach may reduce the duration of active inflammation in UC and hence reduce overall morbidity, future colorectal cancer risk, and requirement for surgery.

For a treat-to-target approach to be utilised, a treatment endpoint must initially be determined. Various treatment endpoints had been proposed in UC. The Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) consensus defines immediate, intermediate and long-term treatment endpoints for IBD[4]. Among UC patients immediate treatment targets include symptomatic response (decrease patient reported outcomes 2 score (PRO2) by at least 50%, or paediatric ulcerative colitis activity index (PUCAI) by at least 20 points). Intermediate term treatment goals include clinical remission (PRO2 of 0, partial Mayo score of < 3 with no sub-score > 1, and in children PUCAI < 10) and normalisation of C reactive protein (CRP) and faecal calprotectin. Long-term treatment goals include endoscopic healing [Mayo endoscopy score (MES) = 0 or ulcerative colitis endoscopic index of severity (UCEIS) ≤ 1], absence of disability, normalized health-related quality of life and normal growth in children. Histologic remission was not recommended as a formal treatment endpoint based on expert opinion of available evidence for either UC or CD. However, the committee did advise that histologic remission may be considered in UC as a deeper level of remission.

There are several issues with the STRIDE-II recommendations. Since the consensus further evidence has emerged related to treatment endpoints in UC. Also, a uniform recommendation of treatment endpoints may not be the best in all UC cases. Furthermore, it needs to be recognised that altering therapy to pursue deeper levels of remission can expose patients to medicating related adverse events and clinical disease relapse. We will seek to address these issues in our article and suggest a practical approach to selecting treatment endpoints in UC.

**Risks of delays in achieving remission in UC**

There are several risks of ongoing active inflammation in UC. Active UC disease symptoms negatively impacts quality of life and disability in UC[5-8]. The time spent with symptomatic disease is increased with delays in achieving disease remission, failure to prevent disease flares and the duration of disease flares. These factors would all culminate to increase overall morbidity of UC over time. A treat-to-target approach using defined treatment endpoints is expected to offer tight disease control, and this would hopefully reduce morbidity over time.

Prolonged time with active UC may have negative consequences for future disease related clinical outcomes. It is unclear if prolonged duration of active disease can impact response to future therapies in UC. Longer disease duration in CD is associated with reduced response to Vedolizumab[9]. However this trend was not observed with UC. Also, time between diagnosis and start of infliximab therapy has not been associated with response to infliximab in IBD[10]. However, prolonged time spent with active inflammation may result in accumulation of permanent bowel damage that can contribute to symptoms even after control of inflammation is achieved in future. Patients with UC have reduced rectal compliance and hypersensitivity compared to healthy controls, and this has been postulated as a significant mechanism for faecal urgency[11,12]. In one study normalisation of histology in UC, was associated with normalisation of rectal compliance as compared to healthy controls[11]. However dysmotility can persist in quiescent UC[13]. This may relate to damage accumulated during active UC, including submucosal fibrosis and muscularis mucosae thickening, which may contribute to persistent dysmotility in UC[14]. Prolonged time spent with active inflammation may be a significant to ongoing functional symptoms in UC, even if durable remission is eventually achieved in future.

Delays in reducing inflammation can also increase risk of future complications in UC. Histologic disease remission has been demonstrated to reduce risk of colorectal cancer development in UC patients[15]. Similarly endoscopic mucosal healing was found to significantly reduce colectomy risk in a Norwegian cohort study of UC patients[16]. Prolonged time with active inflammation may be a factor that increases risk of colorectal cancer and requirement for colectomy in UC.

Prolonged active disease may also result in phenotypic changes in UC that can impact overall morbidity. Proximal disease extension in UC occurs in 27%-54% of UC patients[3]. Studies show that it is associated with increased risks of colectomy, hospitalisation and colorectal cancer. In one study of UC proctitis patients, on multivariate analysis refractory disease (defined as ≥ 3 relapses per year or chronic active disease despite medical therapy) was the only risk factor for proximal disease extension[17]. This indicates early tight disease control may reduce risk of proximal disease extension, and the morbidity that would be associated with same. A Swiss IBD cohort study found that delays in initiating UC therapy is associated with increased risk of UC related complications, predominantly extraintestinal manifestations and extraintestinal complications[18].

Active UC can have immune consequences that directly increase susceptibility to infection, further adding to overall morbidity. In a nationwide Swedish study using longitudinal data, histologic disease activity compared to remission was associated with increased risk of infection in both UC [adjusted hazard ratio (aHR) 1.68; 95% confidence interval (95%CI), 1.51-1.87] and CD (aHR, 1.59; 95%CI, 1.40-1.80)[19]. This trend remained significant even after adjusting for age, sex, education level as well as IBD-related medications. Hence risk of infection increases with active inflammation, not just with IBD-related treatment. Patients hospitalised with UC are likely at an even higher risk of infection owing to both aggressive therapies used as well as active inflammation. In a Japanese observational cohort study, 221 hospitalised acute severe ulcerative colitis (ASUC) patients were followed up[20]. A total of 73 adverse events were recorded. Most adverse events were related to infection (*n* = 39) of which cytomegalovirus (CMV) reactivation was the most common (*n* = 21).

**Treatment end points in Ulcerative colitis**

Treatment endpoints for a treat to target approach should be selected based on their ability to predict for short- and long- term clinically important outcomes. Although treatment endpoints may predict for clinically important outcomes, they themselves are not necessarily clinically important outcomes. In general, clinically important outcomes include symptomatic remission, mortality, disability, quality of life, need for hospitalisation and surgery. Remission as defined by endoscopic, histologic, biochemical, radiologic or functional gut barrier assessments themselves are not clinically important outcomes. However, their ability to predict for clinically important outcomes in the short- and long-term needs to be validated. It would only be appropriate to strive to achieve various treatment endpoints if they can predict for clinically important outcomes.

Studies have found IBD to be associated with no or very small increased risk of overall mortality[21,22]. However IBD overall has a significant impact on quality of life compared to healthy controls, and this is further deteriorated by active disease[5,6]. IBD is also associated with significant disability[7,8]. IBD endpoints should hence be chosen such that they predict for reduced short- and long-term morbidity associated with IBD.

***Clinical remission***

Symptomatic remission is both a treatment endpoint as well as a clinically relevant outcome. Hence patient reported outcomes have formed part of the composite treatment endpoints recommended by the STRIDE-II consensus[4,23]. However clinical remission alone has poorer predictive value for future symptomatic flares, bowel cancer risk and need for surgery compared to endoscopic or histologic remission in UC[24]. On its own clinical remission is hence an insufficient treatment endpoint.

***Endoscopic response and remission***

Various endoscopic scoring systems have been utilised to assess for endoscopic response and remission in UC. The MES is widely most used clinically. Endoscopic remission is generally defined as MES of 0 or 1, whereas mucosal healing is defined as MES 0[23]. The UCEIS, and degree of ulcerative colitis burden of luminal inflammation (DUBLIN) scores are two additional indices that have been employed. In a cohort of patients treated with vedolizumab, post-therapy UCEIS score was superior at predicting clinical outcomes including requirement for surgery and treatment escalation compared to MES and DUBLIN score[25]. UCEIS is more objective and has greater reproducibility than the MES, however it does require the score to be calculated from sub-scores of 3 different parameters, and for each segment of bowel. It can hence be more time consuming to use clinically. In addition, the equipment used (*e.g.* 4K resolution, greater levels of magnification) can result in greater degree of inflammation being detected endoscopically[26].

Endoscopic remission is recognised as a more robust treatment endpoint than clinical remission. In asymptomatic UC patients, MES ≥ 1 predicts for future symptomatic flares[27]. A cohort study from Norway demonstrated that UC patients achieving endoscopic mucosal healing have far reduced risk of colectomy, compared to those that do not[16]. Similarly, early mucosal healing with infliximab therapy in UC was found to significantly predict for colectomy free survival, clinical remission and steroid free clinical remission[28]. A case control study found that achieving endoscopic healing in long standing ulcerative colitis, returned colorectal cancer risk to that of the general population[29].

***Histologic response and remission***

Currently there is no standardised histologic activity scoring that is universally adopted in UC. Several histologic scoring systems have been utilised in UC, including Robarts Histopathology Index (RHI), Geboes score and the Nancy Histological Index (NHI). The RHI and the Geboes score outperform the NHI in their ability to predict for full Mayo score, partial Mayo score and Mayo sub-scores at 52 wk[30]. These can be complex to report by histopathologists, which has precluded wider use. The Paddington International virtual ChromoendoScopy ScOre (PICaSSO) Histological Remission Index (PHRI) has been proposed as a simplified histologic remission index that score remission only on presence of neutrophils. The PHRI has similar predictive value for clinical disease flare at 2 years, as the NHI and the RHI[31]. Artificial intelligence has also been utilised in PHRI scoring of histology samples to reduce pathologist time and ease its implementation[32].

Several recent studies have compared endoscopic and histologic remission and their ability to predict for clinically important outcomes. In a retrospective Australian study, both endoscopic and histologic remission predicted for clinical relapse-free survival. However, on multivariate analysis only histologic remission (defined as NHI < 2) remained as a statistically significant predictor for relapse free survival[33]. Similarly, an interim analysis of a prospective trial of vedolizumab-treated UC patients found that histology remission (defined as NHI = 0), was associated with significantly reduced relapse risk[34]. A meta-analysis of 10 studies involving patients in endoscopic mucosal healing (MES = 0), found that accompanying histologic remission was associated with 63% lower clinical relapse risk compared to those with persistent histologic activity[35]. In a study of a prospectively maintained registry, the impact of histologic disease activity on clinical relapse risk was assessed among patients with endoscopic remission. Patients with complete histologic normalisation were less likely to experience relapse over the 2 year follow up period (12% *vs* 50%)[36]. In another study of 76 UC patients with endoscopically quiescent disease, active histologic inflammation was associated with increased risk of clinical relapse at 18 months, and reduced time to clinical relapse[37]. Histologic inflammation remained a significant predictor of relapse on multivariate analysis. Similarly, in a prospective cohort study from South Korea, patients both in clinical remission (partial Mayo score ≤ 1) and endoscopic remission (UCEIS ≤ 1) were followed up. Those with no histologic activity on rectal biopsies had significantly reduced risk of clinical relapse during a median follow up of 42 wk[38]. Another study found that among UC patients in endoscopic remission (MES of 0 or 1), RHI > 3 predicted for future symptomatic relapse[39]. These studies indicate that histologic remission is superior to endoscopic remission in predicting clinical relapse-free survival in UC.

Achieving histologic remission can further reduce risk of colorectal cancer among UC patients. A case-control study assessed the association between persistent histologic activity and development of high grade-dysplasia (HGD)/colorectal cancer among UC patients with extensive disease who had achieved endoscopic mucosal healing[40]. Participants with UC for 20 years at least and at least 3 surveillance colonoscopies and biopsies after the first 10 years since their UC diagnosis were included. Cases that developed HGD/colorectal cancer compared to controls with no HGD/colorectal cancer, had a greater proportion of colonoscopies demonstrating histologic disease activity (88% *vs* 59%) and lower proportion of participants with no histologic disease activity on any of the prior colonoscopies (15% *vs* 77%).

Recently endocytoscopy, and confocal laser endomicroscopy (CLE) have been utilised as means of assessing histology during endoscopy. These techniques offer up to 1000-fold magnification and permit limited subepithelial imaging[26]. Several studies have demonstrated strong correlation with histologic indices, and improved ability to predict for clinically important outcomes compared to endoscopic mucosal healing[41,42]. However, as a purely imaging technique these modalities may add little if anything compared to conventional histology in terms of ability to predict for clinically important outcomes. There is also a requirement for specialised equipment, with associated startup and ongoing maintenance costs. They may however allow for functional assessment of the gut barrier function, as a completely unique treatment endpoint that should be considered separately.

***Biomarker response and remission***

Given the inconvenience associated with endoscopy and histology to both patients and health care resources, additional non-invasive markers are required which can be utilised more frequently. Faecal calprotectin, erythrocyte sedimentation rate and CRP are most widely used biomarkers in UC. Although these do corelate with endoscopic and histologic disease activity, faecal calprotectin shows the strongest correlation[43-46]. Oher biomarkers such as Leucine-Rich Alpha-2-Glycoprotein, interleukin-6 and faecal lactoferrin, also correlate with endoscopic disease activity, however they are less widely used and do not appear to necessarily outperform faecal calprotectin[47-49]. A very low faecal calprotectin correlates strongly with inactive disease on endoscopy and histology and can be used to monitor for endoscopic disease flares in asymptomatic individuals. Normalisation of faecal calprotectin on infliximab induction has been shown to predict for clinical remission at 1 year and also for endoscopic healing[50]. An elevation in serum faecal calprotectin on consecutive measurements in an otherwise asymptomatic individual has been shown to predict for future symptomatic flare[51]. This is a useful means of monitoring asymptomatic UC patients. It can detect subclinical relapse and allow for interventions to take place to potentially prevent symptom flares which impact on quality of life and contribute to disability.

***Radiologic response and remission***

Intestinal ultrasound (IUS) has recently emerged as a point-of-care means of assessing for bowel wall inflammation. Intestinal ultrasound parameters of increase in bowel wall thickness (BWT) and colour Doppler signal, correlate with endoscopic disease activity[52]. In addition to biomarkers, this can form part of a short to medium term treatment endpoint after starting or modifying therapy to predict future response to therapy, and hence achievement of clinically important outcomes long-term. In a study of 51 UC patients, week 6 IUS parameters of BWT ≤ 3 mm and colour Doppler signal predicted for endoscopic remission and improvement respectively at endoscopy at weeks 8-26[53]. In addition a week 12 intestinal ultrasound Milan ultrasound criteria (MUC) ≤ 6.2, predicted endoscopic improvement at reassessment (defined as MES ≤ 1), where as a MUC cut off of ≤ 4.3 was most accurate cut off for predicting endoscopic remission (defined as MES = 0). On univariate analysis of parameters at week 12 (MUC, faecal calprotectin, CRP and partial Mayo score), both MUC and faecal calprotectin were significant predictors of week 12 endoscopic improvement. However, on multivariate analysis MUC was the only independent predictor.

Intestinal ultrasound avoids the inconvenience to patients associated with undergoing colonoscopy to allow for endoscopic and histologic disease assessment. In addition to biomarkers intestinal ultrasound can be used to monitor asymptomatic UC patients, to detect bowel wall inflammation prior to symptomatic relapse. MUC > 6.2 was shown to predict for future clinical relapse in UC[27]. Interventions during asymptomatic bowel wall inflammation flares can potentially avoid symptomatic relapse, with subsequent impacts on quality of life and overall disability.

***Gut barrier function normalisation as treatment endpoint***

Recently *in vivo* means of assessing gut barrier function have become available. Apart from CLE providing a means to assess for histologic changes at times of endoscopy, it can also provide a measure of intestinal gut barrier function through detection of “gut leak” of IV administered fluorescein. Assessment of gut barrier function can be an additional treatment endpoint that can predict for future clinically relevant outcomes. A prospective cohort study of UC patients in clinical remission, assessed various predictors for development of major adverse outcomes over a mean follow up of 25 months[54,55]. Major adverse outcomes were defined as disease relapse, UC-related hospitalisation, UC-related surgery, initiation or dose escalation of therapy. Ileal barrier healing as assessed by CLE-detected fluorescein leak was superior to endoscopic and histologic remission at predicting for major adverse outcome-free survival. The major drawback to CLE is requirement for specialised equipment and techniques that limits its accessibility at present.

***Quality of life, disability and nutrition***

Although active inflammation directly impacts quality of life in UC, it is not the only aspect to affect this. Functional gut symptoms occur commonly in UC patients and negatively impact quality of life[56]. Similarly, depression, anxiety and fatigue occur at high rates amongst UC patients, and may persist after active disease inflammation is brought under control[57-59]. Sexual function, body image and food enjoyment are other aspects of quality of life (QoL) that may be important for individual patients. Various aspects of QoL and disability may be impacted by both disease as well as treatments. A Japanese study did find reduced sexual function with ileal-pouch formation in UC[60]. QoL and disability are both an important long term treatment endpoint for patients as well as a clinically important outcome, that go beyond controlling active inflammation. IBD specific indices to assess these include the IBD Questionnaire and IBD disability index[61,62]. Treatment selection must also factor in quality of life and disability in addition to efficacy in active inflammation. Physicians may need to engage multidisciplinary approach to address quality of life issues such as mental health, food enjoyment and sexual function.

Although in UC the absorptive capacity of the gastrointestinal tract may not be affected, active inflammation in general induces anorexia, catabolism and sarcopenia[63]. In addition, colonic inflammation in UC can lead to protein loss, further exacerbating sarcopenia and cachexia[64]. Sarcopenia has been linked to fatigue and reduced quality of life in IBD[59]. As such the general nutritional status and overall quality of life needs to be addressed alongside treatment of active inflammation. A dietitian can aid in food selection to improving macro and micronutrient intake. Monitoring on nutrition parameters such as weight, serum albumin and micronutrients, is important to assess the effectiveness of interventions. In children, active inflammation and malnutrition can compound each other to reduce growth velocity and final height attained[65]. As such, correction of both inflammation and malnutrition is of even greater consequence in children, with potential for lifelong repercussions if the growth window period is missed.

***Composite endpoints***

Various endpoints may be independent predictors of future clinically relevant outcomes. Hence combining endpoints may improve prediction of future clinically important outcomes. In one study endoscopic remission and histologic remission were independent predictors for relapse-free-survival at 1 year[66]. Pancolonic UCEIS assessment outperformed original segment UCEIS and worst affected UCEIS. Composite remission endpoint of pancolonic UCEIS ≤ 3 and Geboes score ≤ 3.0 was 92% sensitive and 97% specific at predicating lack of symptomatic relapse at 1 year.

In CD, combined endoscopic and radiologic remission, termed transmural remission, reduced risk of hospitalisation, surgery, steroid use and treatment escalation over a 5-year period[67]. This was a better predictor for clinically important outcomes over a 5 year period, compared to isolated endoscopic remission or isolated radiologic remission. It is unclear if in UC radiologic remission as assessed by IUS or magnetic resonance imaging, would also further improve the ability of endoscopic and histologic remission to predict for clinically important outcomes. The classic teaching that UC is an autoinflammatory condition limited to the mucosal layer of the bowel, is not entirely true. Evidence indicates that UC also involves the submucosa and mucosal layers, with accumulation of progressive damage[14].

Treatment endpoints also need to take into account their accessibility and practicality. Colonoscopies inconvenience patients with requirement for bowel prep and time taken off from work, family and social activities in order to undergo bowel preparation, the procedure itself, and subsequent recovery from the procedure and sedation. In addition, this places a burden on healthcare resources. It would not be convenient to repeat colonoscopies very frequently and as such alternate endpoints are required to supplement endoscopic, histologic and potentially gut barrier function related endpoints. Biomarkers and intestinal ultrasound are used as additional treatment endpoints that can complement clinical assessment. These can be repeated more frequently than endoscopic and histologic assessment to ensure patients are tracking along a desired trajectory.

**Incremental benefit of deeper levels of remission and the risks of their pursuit**

Although population studies have demonstrated superiority of histologic remission and gut barrier function restoration compared to endoscopic remission, it may not be practical to achieve these endpoints in every patient. Local availability of histologic disease activity scoring and/or specialised CLE equipment and expertise would have a bearing on whether these treatment endpoints are to be utilised. In addition, colonoscopy procedural time and healthcare resource constraints would impact the decision to pursue histologic remission and barrier healing as treatment endpoints in addition to endoscopic remission and mucosal healing.

During patient consultations it is important to quantify the incremental benefits of pursuing deeper levels of remission, to allow for informed decision making between patient and clinician. A systematic review by Yoon *et al*[35] assessed the incremental benefits of achieving deeper levels of remission through pooled data from 17 studies, involving some 2608 patients. Achieving MES 0 *vs* 1 was associated with half the clinical relapse risk (28.7% at 12 month for MES 1 *vs* 13.7% for MES 0). Of those that achieved endoscopic remission with MES of 0, achievement of histologic remission further reduced the risk of symptomatic relapse by 63%. The absolute risk of clinical relapse was 13.7% among those with endoscopic remission, compared to 5.0% for those achieving both endoscopic and histologic remission. Absolute risk is a more relevant statistic for communicating risk to patients compared to relative risk.

Careful balancing of risk and benefit of pursuing deeper levels of remission is required. In a treat-to-target approach, patients that are not meeting the desired endpoints are required to have treatment modified by either intensification of current treatments, addition of new treatments, or a change to a different treatment. Any of these 3 changes in therapy has potential to bring about new side effects. Hence careful discussion with the patient is required so that risks and benefits can be weighed. Overall, the safety profile of various advanced IBD therapies is not drastically different. In a network meta-analysis there was no difference between overall rates of adverse events and serious adverse events between biologics, advanced small molecules, microbiome therapies and placebo, apart from an increased risk of overall adverse events with of upadacitinib compared to both infliximab (Odds ratio (OR) 3.36, 95%CI 1.00, 10.36) and adalimumab (OR 4.57, 95%CI 1.02, 19.37)[68]. In another network analysis there was no statistically significant difference between adverse events, serious adverse events and infections between different biologics and also placebo used in UC[69]. Patients and clinicians may place different emphasis on the risk profile of various IBD therapies.

In addition, changing therapy, such as to a new advance therapy, biologic or small molecule, may result in disease flare, with subsequent failure to recapture response on changing to the initial advance therapy. A study of tofacitinib retreatment among responders and remitters in whom treatment was interrupted, found a 74.0% clinical response rate and a 39.0% clinical remission rate[70]. Similarly retreatment with infliximab in prior remitters in whom treatment was interrupted, does not have universal response rate. A study found that recapture of response in this group was 91% post re-induction and 77.5% at 1 year[71]. It is a difficult choice to change therapy in an individual that has had a partial response to one therapy, but has not reached the predetermined treatment endpoint. The number of remaining advance therapies the patient has, as well as their disease phenotype, may impact the decision to pursue deeper levels of remission. Patients with a prior aggressive phenotype, particularly ASUC, who have achieved partial response, may be more reluctant to have their therapy altered.

**Practical recommendations**

We propose an additional arm to the classic treat-to-target algorithm (Figure 1). If a treatment endpoint is not achieved, we propose that the treatment endpoint be reassessed prior to modifying therapy. The decided treatment endpoints should be clearly documented in the patients notes both at the start of therapy and at each assessment thereafter. This ensures that assessment of treatment endpoint appropriateness, and not only their achievement, becomes a routine and formal part of patient assessment.

The clinician cannot treat the UC in isolation and needs to take into account the patients other health issues and priorities. Among patients with limited life expectancy, symptomatic remission may be a sufficient treatment end-point. Long term complications such as dysplasia become less relevant in this case. Depending on the patient co-morbidities, stronger systemic immunosuppression may not be desired.

Furthermore, the timeframe to reassess various endpoints needs to be appropriately selected. This timeframe would depend both on the treatment that has been commenced as well as the selected endpoint. STRIDE-II does provide a consensus on the evidence for mean times to achieve various treatment endpoints in CD and UC, as stratified by treatment (Table 1)[4]. However the authors acknowledge the evidence on which this is based has deficiencies. For various biologics the mean time to achieve mucosal healing in UC was estimated to range between 13 and 18 wk. In a prospective trial of IUS during induction therapy for UC, reduction in BWT as measured by intestinal ultrasound reached statistical significance at week 2 for infliximab and tofacitinib and week 6 for vedolizumab[53]. During short-term follow up it would be more appropriate to assess intestinal ultrasound and biomarkers response rather than endoscopic mucosal healing.

In addition, the practicality of various treatment endpoints needs to be considered. This may impact the time frame over which certain tests could be performed, or whether they can be performed at all. Repeating colonoscopy is potentially more onerous for patients and the healthcare setting compared to clinical assessment, point of care intestinal ultrasound or biomarkers assessment. This would impact the frequency with which colonoscopy is repeated. Although some studies have demonstrated superiority of gut barrier function restoration as a treatment endpoint over endoscopic or histologic remission, requirement for specialised CLE equipment and expertise would have a bearing on whether these treatment endpoints are to be utilised.

Another way of approaching this is to determine the appropriate follow up intervals for an individual patient, and to subsequently determine the endpoints that will be assessed at each follow up interval. A patients disease severity may necessitate closer follow up intervals to ensure the patient is improving along an appropriate trajectory. For instance, post hospitalisation with ASUC would require follow up over a shorter interval compared to post initiation of 5-aminosalicylate therapy for mild UC. Realistic treatment endpoints need to be selected for each follow up interval. It also needs to be recognised that the different individuals would respond to therapies at different rates. It is important not to discontinue therapy too early, particularly if there is evidence of partial response.

Furthermore, in deciding endpoints for an individual patient, we suggest that two separate endpoint thresholds be decided on and documented, this being minimal endpoints and ideal endpoints to be achieved at the appropriate follow up (Table 2). Patients that have partially achieved the minimum treatment endpoints but fall short of achieving the ideal treatment endpoints may have treatment modified if appropriate to achieve these more stringent endpoints. Options to modify therapy would be dose escalation of current therapy, additional of another therapy, or change from current line of therapy to another line of therapy. The last option runs the risk of loss-of-response to the new line of therapy, and potentially failure to recapture response on changing back to the original therapy. This can be of concern in patients with a previous aggressive disease phenotype. With balancing risk and benefit, we may also consider treatment de-escalation in patients that have achieved the ideal treatment endpoint after an appropriate timeframe. Ultimately deciding on treatment endpoints and how hard to pursue them would be a risk and benefit discussion between patient and doctor.

In an otherwise healthy adult patient, we suggest clinical response, biochemical response and IUS response as minimal short-term treatment endpoints. In this time frame we would consider clinical, biochemical and IUS remission as ideal endpoints. At medium term follow up we generally consider clinical remission, biochemical remission, IUS response and endoscopic response as minimal endpoints with IUS and endoscopic remission being considered as ideal endpoints at this follow up. In the long term we would pursue endoscopic remission and histologic response as minimal endpoints, along with normalisation of quality of life and absence of disability. Ideally however given new evidence of improved outcomes with histologic remission and gut barrier function restoration over endoscopic remission, if practical we would consider these as ideal long-term endpoints.

It is important to recognised that conditions other than UC-related autoinflammation may cause treatment endpoints not to be met. If treatment endpoints are not met the clinician should also consider and if necessary, treat any such underlying conditions in a treat-to-target approach, rather than mechanistically altering IBD related therapy. A significant proportion of IBD patients have functional bowel symptoms which can persist even if inflammation is controlled, and can manifest symptomatically similar to disease flare[56]. Infection such as CMV or Clostridium difficile, may also drive inflammation instead of or alongside UC related auto-inflammation[72-74]. These are hence important to diagnose and treat.

**Future research directions**

Future research should focus on working out the ideal combination of treatment endpoints that are validated against short and long-term clinically relevant outcomes. We need to understand which endpoints predict for clinically important outcomes independently, such that we are not pursuing treatment endpoints that add little to the total predictive value. This would achieve best value healthcare for patients. In addition, we need studies that quantify the additional benefit of achieving more stringent treatment endpoints, such that an informed risk and benefit discussion can be had with patients in order to decide on appropriate treatment endpoints within an individual patient. Further studies are required to quantify the ideal time frame to assess for various treatment endpoints, depending on the initiated therapy. As there is inter-individual variability in rates of response to various therapies, studies are also needed to determine time frame for plateau of attainment of various treatment endpoints. This will clarify a time frame beyond which persisting with a particular therapy becomes futile, relative to the treatment endpoint chosen. Studies should also focus on modifying factors within individual patients that may make certain treatment endpoints more relevant.

The above multidimensional model for selecting individualised treatment endpoints and the time frames over which they are to be assessed, may become more complex as further data becomes available. Machine based learning has been shown to outperform traditional statistical modelling in risk prediction models in IBD[75]. Computer modelling may be utilised in future to aid in risk and benefit discussions in individual patients when deciding on pursuing deeper levels of remission.

**CONCLUSION**

To conclude treatment endpoints in UC is not a one size fits all unfortunately. We suggest that treatment endpoints should be individually decided upon through discussion between patient and physician. Treatment endpoints should not be a set-and-forget target, but should be regularly re-evaluated for appropriateness within an individual patient. We suggest the addition of histologic remission and gut barrier function restoration, depending on accessibility, as long-term treatment endpoints in UC to the latest STRIDE-II recommendations. However, individual patient circumstances may warrant relaxation of treatment endpoints. Similarly, within individuals treatment endpoints should be treated as a spectrum with two thresholds being set. For each time-frame of short-, medium- and long-term treatment endpoints, both minimum and ideal treatment endpoint thresholds should be set. Not achieving the minimum treatment endpoints would usually necessitate treatment modification. However, achieving the minimum but not the ideal endpoints may warrant less drastic treatment modification such as dose up-titration, addition of another treatment, but potentially not changing to another advanced therapy. Although delineating treatment endpoints for every potential patient circumstance is beyond the scope of this editorial, we have presented considerations that should be taken into account in deciding on treatment endpoints. Further studies are required to provide a stronger evidence basis for selecting treatment endpoints in individuals.

**REFERENCES**

1 National Collaborating Centre for Chronic Conditions. Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults. London: Royal College of Physicians, 2009

2 **Colombel JF**, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, Danalioglu A, Novacek G, Armuzzi A, Hébuterne X, Travis S, Danese S, Reinisch W, Sandborn WJ, Rutgeerts P, Hommes D, Schreiber S, Neimark E, Huang B, Zhou Q, Mendez P, Petersson J, Wallace K, Robinson AM, Thakkar RB, D'Haens G. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2017; **390**: 2779-2789 [PMID: 29096949 DOI: 10.1016/S0140-6736(17)32641-7]

3 **Torres J**, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis* 2012; **18**: 1356-1363 [PMID: 22162423 DOI: 10.1002/ibd.22839]

4 **Turner D**, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, Bettenworth D, Sandborn WJ, Sands BE, Reinisch W, Schölmerich J, Bemelman W, Danese S, Mary JY, Rubin D, Colombel JF, Peyrin-Biroulet L, Dotan I, Abreu MT, Dignass A; International Organization for the Study of IBD. 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 [PMID: 33359090 DOI: 10.1053/j.gastro.2020.12.031]

5 **Knowles SR**, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part I. *Inflamm Bowel Dis* 2018; **24**: 742-751 [PMID: 29562277 DOI: 10.1093/ibd/izx100]

6 **Knowles SR**, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part II. *Inflamm Bowel Dis* 2018; **24**: 966-976 [PMID: 29688466 DOI: 10.1093/ibd/izy015]

7 **Ramos A**, Calvet X, Sicilia B, Vergara M, Figuerola A, Motos J, Sastre A, Villoria A, Gomollón F. IBD-related work disability in the community: Prevalence, severity and predictive factors. A cross-sectional study. *United European Gastroenterol J* 2015; **3**: 335-342 [PMID: 26279841 DOI: 10.1177/2050640615577532]

8 **Tannoury J**, Nachury M, Martins C, Serrero M, Filippi J, Roblin X, Bourrier A, Bouguen G, Franchimont D, Savoye G, Buisson A, Louis E, Nancey S, Abitbol V, Reimund JM, DeWitt O, Vuitton L, Mathieu N, Peyrin-Biroulet L, Gilletta C, Allez M, Viennot S, Trang-Poisson C, Laharie D, Amiot A; GETAID-Patient Experience Study Group. Determinants of IBD-related disability: a cross-sectional survey from the GETAID. *Aliment Pharmacol Ther* 2021; **53**: 1098-1107 [PMID: 33817819 DOI: 10.1111/apt.16353]

9 **Faleck DM**, Winters A, Chablaney S, Shashi P, Meserve J, Weiss A, Aniwan S, Koliani-Pace JL, Kochhar G, Boland BS, Singh S, Hirten R, Shmidt E, Kesar V, Lasch K, Luo M, Bohm M, Varma S, Fischer M, Hudesman D, Chang S, Lukin D, Sultan K, Swaminath A, Gupta N, Siegel CA, Shen B, Sandborn WJ, Kane S, Loftus EV Jr, Sands BE, Colombel JF, Dulai PS, Ungaro R. 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 [PMID: 30625408 DOI: 10.1016/j.cgh.2018.12.040]

10 **Martins CA**, de Azevedo MFC, Carlos AS, Damião AOMC, Sobrado Junior CW, Nahas SC, Queiroz NSF. Predictive factors of response to infliximab therapy in Brazilian inflammatory bowel disease patients. *Therap Adv Gastroenterol* 2023; **16**: 17562848231210053 [PMID: 38026104 DOI: 10.1177/17562848231210053]

11 **Krugliak Cleveland N**, Rai V, El Jurdi K, Rao SS, Giurcanu MC, Rubin DT. Ulcerative Colitis Patients Have Reduced Rectal Compliance Compared With Non-Inflammatory Bowel Disease Controls. *Gastroenterology* 2022; **162**: 331-333.e1 [PMID: 34597674 DOI: 10.1053/j.gastro.2021.09.052]

12 **Rao SS**, Read NW, Davison PA, Bannister JJ, Holdsworth CD. Anorectal sensitivity and responses to rectal distention in patients with ulcerative colitis. *Gastroenterology* 1987; **93**: 1270-1275 [PMID: 3678745 DOI: 10.1016/0016-5085(87)90255-1]

13 **Loening-Baucke V**, Metcalf AM, Shirazi S. Rectosigmoid motility in patients with quiescent and active ulcerative colitis. *Am J Gastroenterol* 1989; **84**: 34-39 [PMID: 2912029]

14 **Gordon IO**, Agrawal N, Willis E, Goldblum JR, Lopez R, Allende D, Liu X, Patil DY, Yerian L, El-Khider F, Fiocchi C, Rieder F. Fibrosis in ulcerative colitis is directly linked to severity and chronicity of mucosal inflammation. *Aliment Pharmacol Ther* 2018; **47**: 922-939 [PMID: 29411405 DOI: 10.1111/apt.14526]

15 **Rubin DT**, Huo D, Kinnucan JA, Sedrak MS, McCullom NE, Bunnag AP, Raun-Royer EP, Cohen RD, Hanauer SB, Hart J, Turner JR. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. *Clin Gastroenterol Hepatol* 2013; **11**: 1601-8.e1-4 [PMID: 23872237 DOI: 10.1016/j.cgh.2013.06.023]

16 **Frøslie KF**, Jahnsen J, Moum BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]

17 **Meucci G**, Vecchi M, Astegiano M, Beretta L, Cesari P, Dizioli P, Ferraris L, Panelli MR, Prada A, Sostegni R, de Franchis R. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). *Am J Gastroenterol* 2000; **95**: 469-473 [PMID: 10685752 DOI: 10.1111/j.1572-0241.2000.t01-1-01770.x]

18 **Manser CN**, Borovicka J, Seibold F, Vavricka SR, Lakatos PL, Fried M, Rogler G; investigators of the Swiss Inflammatory Bowel Disease Cohort Study. Risk factors for complications in patients with ulcerative colitis. *United European Gastroenterol J* 2016; **4**: 281-287 [PMID: 27087958 DOI: 10.1177/2050640615627533]

19 **Mårild K**, Söderling J, Axelrad J, Halfvarson J, Forss A; SWIBREG Study Group, Olén O, Ludvigsson JF. Histologic Activity in Inflammatory Bowel Disease and Risk of Serious Infections: A Nationwide Study. *Clin Gastroenterol Hepatol* 2023 [PMID: 37913937 DOI: 10.1016/j.cgh.2023.10.013]

20 **Naganuma M**, Kobayashi T, Kunisaki R, Matsuoka K, Yamamoto S, Kawamoto A, Saito D, Nanki K, Narimatsu K, Shiga H, Esaki M, Yoshioka S, Kato S, Saruta M, Tanaka S, Yasutomi E, Yokoyama K, Moriya K, Tsuzuki Y, Ooi M, Fujiya M, Nakazawa A, Abe T, Hisamatsu T; Japanese UC Study Group. Real-world efficacy and safety of advanced therapies in hospitalized patients with ulcerative colitis. *J Gastroenterol* 2023; **58**: 1198-1210 [PMID: 37831183 DOI: 10.1007/s00535-023-02048-w]

21 **Card T**, Hubbard R, Logan RF. Mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology* 2003; **125**: 1583-1590 [PMID: 14724808 DOI: 10.1053/j.gastro.2003.09.029]

22 **Fumery M**, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. *Clin Gastroenterol Hepatol* 2018; **16**: 343-356.e3 [PMID: 28625817 DOI: 10.1016/j.cgh.2017.06.016]

23 **Peyrin-Biroulet L**, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Gearry R, Krishnareddy S, Lakatos PL, Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; **110**: 1324-1338 [PMID: 26303131 DOI: 10.1038/ajg.2015.233]

24 **Parkes G**, Ungaro RC, Danese S, Abreu MT, Arenson E, Zhou W, Ilo D, Laroux FS, Deng H, Sanchez Gonzalez Y, Peyrin-Biroulet L. Correlation of mucosal healing endpoints with long-term clinical and patient-reported outcomes in ulcerative colitis. *J Gastroenterol* 2023; **58**: 990-1002 [PMID: 37490069 DOI: 10.1007/s00535-023-02013-7]

25 **Yan J**, Liu A, Fang L, Wu J, Ding X, Xu Y. The ulcerative colitis endoscopic index of severity score is superior to reflecting long-term prognosis in ulcerative colitis patients treated with vedolizumab. *Medicine (Baltimore)* 2023; **102**: e35799 [PMID: 37933053 DOI: 10.1097/MD.0000000000035799]

26 **Neurath MF**, Vieth M. Different levels of healing in inflammatory bowel diseases: mucosal, histological, transmural, barrier and complete healing. *Gut* 2023; **72**: 2164-2183 [PMID: 37640443 DOI: 10.1136/gutjnl-2023-329964]

27 **Maeda M**, Sagami S, Tashima M, Yamana Y, Karashima R, Miyatani Y, Hojo A, Nakano M, Hibi T, Kobayashi T. Milan Ultrasound Criteria Predict Relapse of Ulcerative Colitis in Remission. *Inflamm Intest Dis* 2023; **8**: 95-104 [PMID: 38098495 DOI: 10.1159/000532052]

28 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID: 21723220 DOI: 10.1053/j.gastro.2011.06.054]

29 **Rutter MD**, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. *Gut* 2004; **53**: 1813-1816 [PMID: 15542520 DOI: 10.1136/gut.2003.038505]

30 **Peyrin-Biroulet L**, Arenson E, Rubin DT, Siegel CA, Lee S, Stephen Laroux F, Zhou W, Finney-Hayward T, Sanchez Gonzalez Y, Shields AL. A Comparative Evaluation of the Measurement Properties of Three Histological Indices of Mucosal Healing in Ulcerative Colitis: Geboes Score, Robarts Histopathology Index and Nancy Index. *J Crohns Colitis* 2023; **17**: 1733-1743 [PMID: 37225135 DOI: 10.1093/ecco-jcc/jjad087]

31 **Parigi TL**, Cannatelli R, Nardone OM, Zammarchi I, Shivaji U, Furfaro F, Zardo D, Spaggiari P, Del Sordo R, Setti O, Majumder S, Smith SCL, Danese S, Armuzzi A, Villanacci V, Ghosh S, Iacucci M. Neutrophil-only Histological Assessment of Ulcerative Colitis Correlates with Endoscopic Activity and Predicts Long-term Outcomes in a Multicentre Study. *J Crohns Colitis* 2023; **17**: 1931-1938 [PMID: 37390319 DOI: 10.1093/ecco-jcc/jjad110]

32 **Gui X**, Bazarova A, Del Amor R, Vieth M, de Hertogh G, Villanacci V, Zardo D, Parigi TL, Røyset ES, Shivaji UN, Monica MAT, Mandelli G, Bhandari P, Danese S, Ferraz JG, Hayee B, Lazarev M, Parra-Blanco A, Pastorelli L, Panaccione R, Rath T, Tontini GE, Kiesslich R, Bisschops R, Grisan E, Naranjo V, Ghosh S, Iacucci M. PICaSSO Histologic Remission Index (PHRI) in ulcerative colitis: development of a novel simplified histological score for monitoring mucosal healing and predicting clinical outcomes and its applicability in an artificial intelligence system. *Gut* 2022; **71**: 889-898 [PMID: 35173041 DOI: 10.1136/gutjnl-2021-326376]

33 **Wang H**, Fewings I, Bornman L, Shadbolt B, Fadia M, Subramaniam K. Histologic Remission (NANCY Index) is Superior to Endoscopic Mucosal Healing in Predicting Relapse Free Survival in Patients With Ulcerative Colitis in Clinical and Endoscopic Remission. *J Clin Gastroenterol* 2023; **57**: 494-500 [PMID: 35220375 DOI: 10.1097/MCG.0000000000001681]

34 **Pudipeddi A,** Fung C, Kariyawasam V, Paramsothy R, Ghaly S, Haifer C, An Y, Begun J, Connor S, Chetwood J, Paramsothy S, Leong RW. DDF2022-ABS-0162 Histological remission using a nancy index of 0 is associated with longer relapse-free survival than histological activity in patients with ulcerative colitis in clinical and endoscopic remission. *Gut* 2022; **71**: A149 [DOI: 10.1136/gutjnl-2022-IDDF.207]

35 **Yoon H**, Jangi S, Dulai PS, Boland BS, Prokop LJ, Jairath V, Feagan BG, Sandborn WJ, Singh S. Incremental Benefit of Achieving Endoscopic and Histologic Remission in Patients With Ulcerative Colitis: A Systematic Review and Meta-Analysis. *Gastroenterology* 2020; **159**: 1262-1275.e7 [PMID: 32585306 DOI: 10.1053/j.gastro.2020.06.043]

36 **Cushing KC**, Tan W, Alpers DH, Deshpande V, Ananthakrishnan AN. Complete histologic normalisation is associated with reduced risk of relapse among patients with ulcerative colitis in complete endoscopic remission. *Aliment Pharmacol Ther* 2020; **51**: 347-355 [PMID: 31696961 DOI: 10.1111/apt.15568]

37 **Kevans D**, Kirsch R, Dargavel C, Kabakchiev B, Riddell R, Silverberg MS. Histological Markers of Clinical Relapse in Endoscopically Quiescent Ulcerative Colitis. *Inflamm Bowel Dis* 2020; **26**: 1722-1729 [PMID: 31883337 DOI: 10.1093/ibd/izz308]

38 **Park J**, Kang SJ, Yoon H, Park J, Oh HJ, Na HY, Lee HS, Shin CM, Park YS, Kim N, Lee DH. Histologic Evaluation Using the Robarts Histopathology Index in Patients With Ulcerative Colitis in Deep Remission and the Association of Histologic Remission With Risk of Relapse. *Inflamm Bowel Dis* 2022; **28**: 1709-1716 [PMID: 35016209 DOI: 10.1093/ibd/izab340]

39 **George LA**, Feldman HT, Alizadeh M, Abutaleb A, Zullow S, Hine A, Stashek K, Sarkar S, Sun K, Hudesman D, Axelrad J, Cross RK. Histologic Inflammation can Predict Future Clinical Relapse in Ulcerative Colitis Patients in Endoscopic Remission. *Crohns Colitis 360* 2023; **5**: otad059 [PMID: 37886705 DOI: 10.1093/crocol/otad059]

40 **Korelitz BI**, Sultan K, Kothari M, Arapos L, Schneider J, Panagopoulos G. Histological healing favors lower risk of colon carcinoma in extensive ulcerative colitis. *World J Gastroenterol* 2014; **20**: 4980-4986 [PMID: 24803809 DOI: 10.3748/wjg.v20.i17.4980]

41 **Maeda Y**, Kudo SE, Mori Y, Misawa M, Ogata N, Sasanuma S, Wakamura K, Oda M, Mori K, Ohtsuka K. Fully automated diagnostic system with artificial intelligence using endocytoscopy to identify the presence of histologic inflammation associated with ulcerative colitis (with video). *Gastrointest Endosc* 2019; **89**: 408-415 [PMID: 30268542 DOI: 10.1016/j.gie.2018.09.024]

42 **Vitali F**, Morgenstern N, Eckstein M, Atreya R, Waldner M, Hartmann A, Neurath MF, Rath T. Endocytoscopy for assessing histologic inflammation in ulcerative colitis: development and prospective validation of the ELECT (ErLangen Endocytoscopy in ColiTis) score (with videos). *Gastrointest Endosc* 2023; **97**: 100-111.e1 [PMID: 36058265 DOI: 10.1016/j.gie.2022.08.023]

43 **Schoepfer AM**, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009; **15**: 1851-1858 [PMID: 19462421 DOI: 10.1002/ibd.20986]

44 **Schoepfer AM**, Beglinger C, Straumann A, Trummler M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; **105**: 162-169 [PMID: 19755969 DOI: 10.1038/ajg.2009.545]

45 **Yoon JY**, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Correlations of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic activity indices in patients with ulcerative colitis. *Dig Dis Sci* 2014; **59**: 829-837 [PMID: 24352705 DOI: 10.1007/s10620-013-2907-3]

46 **Canani RB**, Terrin G, Rapacciuolo L, Miele E, Siani MC, Puzone C, Cosenza L, Staiano A, Troncone R. Faecal calprotectin as reliable non-invasive marker to assess the severity of mucosal inflammation in children with inflammatory bowel disease. *Dig Liver Dis* 2008; **40**: 547-553 [PMID: 18358796 DOI: 10.1016/j.dld.2008.01.017]

47 **Tatsumi Y**, Kakimoto K, Hara A, Mizuta N, Numa K, Kinoshita N, Nakazawa K, Koshiba R, Hirata Y, Ota K, Miyazaki T, Nakamura S, Sakagami K, Arimitsu S, Ito H, Nishikawa H. Biomarkers for Monitoring of Changes in Disease Activity in Ulcerative Colitis. *J Clin Med* 2023; **12** [PMID: 38002777 DOI: 10.3390/jcm12227165]

48 **Hayashi T**, Kitamura K, Usami M, Miyazawa M, Nishitani M, Dejima A, Yamamoto M, Kawase S, Funaki M, Orita N, Nakagawa H, Morita K, Iida N, Seki A, Nio K, Kido H, Takayama H, Takeuchi Y, Yamada S, Takatori H, Shimada M, Saito H, Yamamoto D, Toyama T, Yamashita T. Novel Utility of Leucine-Rich Alpha-2-Glycoprotein as a Biomarker in Ulcerative Colitis: A Predictor of Endoscopic Remission Independent of Symptoms. *Inflamm Intest Dis* 2023; **8**: 133-142 [PMID: 38115911 DOI: 10.1159/000534001]

49 **Chen R**, Li L, Tie Y, Chen M, Zhang S. Trajectory of fecal lactoferrin for predicting prognosis in ulcerative colitis. *Precis Clin Med* 2023; **6**: pbad022 [PMID: 38025971 DOI: 10.1093/pcmedi/pbad022]

50 **Theede K**, Holck S, Ibsen P, Kallemose T, Nordgaard-Lassen I, Nielsen AM. Fecal Calprotectin Predicts Relapse and Histological Mucosal Healing in Ulcerative Colitis. *Inflamm Bowel Dis* 2016; **22**: 1042-1048 [PMID: 26919460 DOI: 10.1097/MIB.0000000000000736]

51 **Ferreiro-Iglesias R**, Barreiro-de Acosta M, Lorenzo-Gonzalez A, Dominguez-Muñoz JE. Accuracy of Consecutive Fecal Calprotectin Measurements to Predict Relapse in Inflammatory Bowel Disease Patients Under Maintenance With Anti-TNF Therapy: A Prospective Longitudinal Cohort Study. *J Clin Gastroenterol* 2018; **52**: 229-234 [PMID: 27984399 DOI: 10.1097/MCG.0000000000000774]

52 **Allocca M**, Fiorino G, Bonovas S, Furfaro F, Gilardi D, Argollo M, Magnoni P, Peyrin-Biroulet L, Danese S. Accuracy of Humanitas Ultrasound Criteria in Assessing Disease Activity and Severity in Ulcerative Colitis: A Prospective Study. *J Crohns Colitis* 2018; **12**: 1385-1391 [PMID: 30085066 DOI: 10.1093/ecco-jcc/jjy107]

53 **de Voogd FA**, Bots SJ, van Wassenaer EA, de Jong M, Pruijt MJ, D'Haens GR, Gecse KB. Early Intestinal Ultrasound Predicts Clinical and Endoscopic Treatment Response and Demonstrates Drug-Specific Kinetics in Moderate-to-Severe Ulcerative Colitis. *Inflamm Bowel Dis* 2023 [PMID: 38011801 DOI: 10.1093/ibd/izad274]

54 **Rath T**, Atreya R, Bodenschatz J, Uter W, Geppert CI, Vitali F, Zundler S, Waldner MJ, Hartmann A, Neurath MF. Healing of the epithelial barrier in the ileum is superior to endoscopic and histologic remission for predicting major adverse outcomes in ulcerative colitis. *Front Med (Lausanne)* 2023; **10**: 1221449 [PMID: 37881628 DOI: 10.3389/fmed.2023.1221449]

55 **Rath T**, Atreya R, Bodenschatz J, Uter W, Geppert CE, Vitali F, Fischer S, Waldner MJ, Colombel JF, Hartmann A, Neurath MF. Intestinal Barrier Healing Is Superior to Endoscopic and Histologic Remission for Predicting Major Adverse Outcomes in Inflammatory Bowel Disease: The Prospective ERIca Trial. *Gastroenterology* 2023; **164**: 241-255 [PMID: 36279923 DOI: 10.1053/j.gastro.2022.10.014]

56 **Halpin SJ**, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2012; **107**: 1474-1482 [PMID: 22929759 DOI: 10.1038/ajg.2012.260]

57 **Cheema M**, Mitrev N, Hall L, Tiongson M, Ahlenstiel G, Kariyawasam V. Depression, anxiety and stress among patients with inflammatory bowel disease during the COVID-19 pandemic: Australian national survey. *BMJ Open Gastroenterol* 2021; **8** [PMID: 33579729 DOI: 10.1136/bmjgast-2020-000581]

58 **Uhlir V**, Stallmach A, Grunert PC. Fatigue in patients with inflammatory bowel disease-strongly influenced by depression and not identifiable through laboratory testing: a cross-sectional survey study. *BMC Gastroenterol* 2023; **23**: 288 [PMID: 37608313 DOI: 10.1186/s12876-023-02906-0]

59 **Tasson L**, Zingone F, Barberio B, Valentini R, Ballotta P, Ford AC, Scarpa M, Angriman I, Fassan M, Savarino E. Sarcopenia, severe anxiety and increased C-reactive protein are associated with severe fatigue in patients with inflammatory bowel diseases. *Sci Rep* 2021; **11**: 15251 [PMID: 34315951 DOI: 10.1038/s41598-021-94685-5]

60 **Yoshida K**, Araki T, Uchida K, Okita Y, Fujikawa H, Inoue M, Tanaka K, Inoue Y, Mohri Y, Kusunoki M. Sexual activity after ileal pouch-anal anastomosis in Japanese patients with ulcerative colitis. *Surg Today* 2014; **44**: 73-79 [PMID: 23440359 DOI: 10.1007/s00595-013-0505-9]

61 **Yarlas A**, Maher S, Bayliss M, Lovley A, Cappelleri JC, Bushmakin AG, DiBonaventura MD. The Inflammatory Bowel Disease Questionnaire in Randomized Controlled Trials of Treatment for Ulcerative Colitis: Systematic Review and Meta-Analysis. *J Patient Cent Res Rev* 2020; **7**: 189-205 [PMID: 32377552 DOI: 10.17294/2330-0698.1722]

62 **Paulides E**, Kim C, Frampton C, Gearry RB, Eglinton T, Leong RW, de Boer NKH, Mulder CJJ, McCombie AM. Validation of the inflammatory bowel disease disability index for self-report and development of an item-reduced version. *J Gastroenterol Hepatol* 2019; **34**: 92-102 [PMID: 30276858 DOI: 10.1111/jgh.14496]

63 **Nardone OM**, de Sire R, Petito V, Testa A, Villani G, Scaldaferri F, Castiglione F. Inflammatory Bowel Diseases and Sarcopenia: The Role of Inflammation and Gut Microbiota in the Development of Muscle Failure. *Front Immunol* 2021; **12**: 694217 [PMID: 34326845 DOI: 10.3389/fimmu.2021.694217]

64 **Ungaro R**, Babyatsky MW, Zhu H, Freed JS. Protein-losing enteropathy in ulcerative colitis. *Case Rep Gastroenterol* 2012; **6**: 177-182 [PMID: 22679407 DOI: 10.1159/000338191]

65 **Hildebrand H**, Karlberg J, Kristiansson B. Longitudinal growth in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1994; **18**: 165-173 [PMID: 8014763 DOI: 10.1097/00005176-199402000-00008]

66 **Kaneshiro M**, Takenaka K, Suzuki K, Fujii T, Hibiya S, Kawamoto A, Motobayashi M, Shimizu H, Nagahori M, Saito E, Okamoto R, Ohtsuka K, Watanabe M. Pancolonic endoscopic and histologic evaluation for relapse prediction in patients with ulcerative colitis in clinical remission. *Aliment Pharmacol Ther* 2021; **53**: 900-907 [PMID: 33645736 DOI: 10.1111/apt.16310]

67 **Fernandes SR**, Serrazina J, Botto IA, Leal T, Guimarães A, Garcia JL, Rosa I, Prata R, Carvalho D, Neves J, Campelo P, Ventura S, Silva A, Coelho M, Sequeira C, Oliveira AP, Portela F, Ministro P, Tavares de Sousa H, Ramos J, Claro I, Gonçalves R, Correia LA, Marinho RT, Cortez-Pinto H, Magro F. Transmural remission improves clinical outcomes up to 5 years in Crohn's disease. *United European Gastroenterol J* 2023; **11**: 51-59 [PMID: 36575615 DOI: 10.1002/ueg2.12356]

68 **Gao J**, Nie R, Chen Y, Yang W, Ren Q. Comparative of the effectiveness and safety of biological agents, small molecule drugs, and microbiome therapies in ulcerative colitis: Systematic review and network meta-analysis. *Medicine (Baltimore)* 2023; **102**: e35689 [PMID: 37904440 DOI: 10.1097/MD.0000000000035689]

69 **Chu X**, Biao Y, Liu C, Zhang Y, Liu C, Ma JZ, Guo Y, Gu Y. Network meta-analysis on efficacy and safety of different biologics for ulcerative colitis. *BMC Gastroenterol* 2023; **23**: 346 [PMID: 37803294 DOI: 10.1186/s12876-023-02938-6]

70 **Panés J**, Vermeire S, Dubinsky MC, Loftus EV, Lawendy N, Wang W, Salese L, Su C, Modesto I, Guo X, Colombel JF. Efficacy and Safety of Tofacitinib Re-treatment for Ulcerative Colitis After Treatment Interruption: Results from the OCTAVE Clinical Trials. *J Crohns Colitis* 2021; **15**: 1852-1863 [PMID: 33884415 DOI: 10.1093/ecco-jcc/jjab065]

71 **Baert F**, Drobne D, Gils A, Vande Casteele N, Hauenstein S, Singh S, Lockton S, Rutgeerts P, Vermeire S. Early trough levels and antibodies to infliximab predict safety and success of reinitiation of infliximab therapy. *Clin Gastroenterol Hepatol* 2014; **12**: 1474-81.e2; quiz e91 [PMID: 24486408 DOI: 10.1016/j.cgh.2014.01.033]

72 **Nguyen GC**, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008; **103**: 1443-1450 [PMID: 18513271 DOI: 10.1111/j.1572-0241.2007.01780.x]

73 **Wong SH,** Tang W, Wu JC, Ng SC. Clostridium difficile infections in inflammatory bowel disease patients is associated with increased use of immunosuppressants and higher rates of colectomy: results from a population-based cohort. Proceedings of the Digestive Diseases Week, 2016

74 **Lee HS**, Park SH, Kim SH, Kim J, Choi J, Lee HJ, Kim WS, Lee JM, Kwak MS, Hwang SW, Yang DH, Kim KJ, Ye BD, Byeon JS, Myung SJ, Yoon YS, Yu CS, Kim JH, Yang SK. Risk Factors and Clinical Outcomes Associated with Cytomegalovirus Colitis in Patients with Acute Severe Ulcerative Colitis. *Inflamm Bowel Dis* 2016; **22**: 912-918 [PMID: 26829410 DOI: 10.1097/MIB.0000000000000675]

75 **Nguyen NH**, Picetti D, Dulai PS, Jairath V, Sandborn WJ, Ohno-Machado L, Chen PL, Singh S. Machine Learning-based Prediction Models for Diagnosis and Prognosis in Inflammatory Bowel Diseases: A Systematic Review. *J Crohns Colitis* 2022; **16**: 398-413 [PMID: 34492100 DOI: 10.1093/ecco-jcc/jjab155]

**Footnotes**

**Conflict-of-interest statement:** All authors declare no conflict-of-interest in the write up of this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Australia

**Peer-review report’s classification**

**Scientific Quality:** Grade B

**Novelty:** Grade B

**Creativity or Innovation:** Grade B

**Scientific Significance:** Grade B

**P-Reviewer:** Ding X, China **S-Editor:** Liu JH **L-Editor:** A **P-Editor:** Zheng XM

**Figure Legends**



**Figure 1 Proposed treat-to-target algorithm where treatment endpoints are a dynamic entity.**

**Table 1 Mean times (in weeks) for various induction therapies to reach a particular endpoint in ulcerative colitis**

|  |  |
| --- | --- |
|  | **Treatment endpoints** |
| **Therapy** | **Clinical response** | **Clinical remission** | **Normalisation CRP/ESR** | **Decrease of faecal calprotectin** | **Mucosal healing** |
| Oral 5-aminosalicylates | 4 | 8 | 8 | 10 | 13 |
| Oral steroids | 2 | 2 | 5 | 8 | 11 |
| Locally acting steroids | 3 | 8 | 8 | 9 | 13 |
| Thiopurines | 11 | 15 | 15 | 15 | 20 |
| Adalimumab | 6 | 11 | 10 | 12 | 14 |
| Infliximab | 5 | 10 | 9 | 11 | 13 |
| Vedolizumab | 9 | 14 | 14 | 15 | 18 |
| Tofacitinib | 6 | 11 | 9 | 11 | 14 |

CRP: C reactive protein; ESR: Erythrocyte sedimentation rate. Adapted from Turner *et al*[4], 2021.

**Table 2 Suggested table for documentation of treatment endpoints in ulcerative colitis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Time frame** | **Short term** | **Medium term** | **Long term** |
| Proposed duration | 6-8 wk | 12-16 wk | 26-52 wk |
| Endpoint type | Minimum endpoints | Ideal endpoints | Minimum endpoints | Ideal endpoints | Minimum endpoints | Ideal endpoints |
| Endpoints | Clinical response; Biochemical response; IUS response | Clinical remission; Biochemical remission; IUS remission | Clinical remission; IUS response; Endoscopic response  | IUS remission; Endoscopic remission  | Endoscopic remission; Histologic response | Endoscopic healing; Histologic healing; Gut barrier function restoration |

It is recommended that endpoints in this table are re-evaluated periodically to either confirm or modify endpoints depending on individual patient factors. The above may be applicable for an otherwise healthy adult with ulcerative colitis. Ideal endpoints are in addition to minimum endpoints. IUS: Intestinal ultrasound.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** office@baishideng.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2024 Baishideng Publishing Group Inc. All rights reserved.**