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Disease clearance in ulcerative colitis: A new therapeutic target for the future

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Abstract

Advancements in murine modeling systems for ulcerative colitis have diversified our understanding of the pathophysiological factors involved in disease onset and progression. This has fueled the identification of molecular targets, resulting in a rapidly expanding therapeutic armamentarium. Subsequently, management strategies have evolved from symptomatic resolution to well-defined objective endpoints, including clinical remission, endoscopic remission and mucosal healing. While the incorporation of these assessment modalities has permitted targeted intervention in the context of a natural disease history and the prevention of complications, studies have consistently depicted discrepancies associated with ascertaining disease status through clinical and endoscopic measures. Current recommendations lack consideration of histological healing. The simultaneous achievement of clinical, endoscopic, and histologic remission has not been fully investigated. This has laid the groundwork for a novel therapeutic outcome termed disease clearance (DC). This article summarizes the concept of DC and its current evidence.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Clinical remission; Endoscopic remission; Histological remission; Mucosal healing; Disease clearance

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Core Tip: Clinical management of ulcerative colitis is guided by a combination of clinical and endoscopic measures, but histologic healing is undervalued. The current definition of disease remission is insufficient due to discrepancies in outcomes. Disease clearance (DC) is a novel emerging composite outcome defined as the simultaneous attainment of clinical, endoscopic and histologic remission. The risk of disease relapse, hospitalization and surgery is significantly lower in patients who achieve DC. It provides superior optimal disease control in the short term. Large prospective studies are needed to determine the cost effectiveness, risk-benefit ratio and impact on long-term outcomes.

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INTRODUCTION

First described by Samuel Wilks in 1859, ulcerative colitis (UC) is a chronic, idiopathic relapsing inflammatory bowel disease (IBD) limited to the large intestine[1]. UC is characterized by chronic inflammation in the rectum and can progress continuously to the proximal colon[2,3]. The underlying etiology of this disease is considered multifactorial, with increasing focus on aberrant immune response, gut dysbiosis, a compromised gut epithelial barrier, genetic susceptibility and environmental factors[4]. Clinically, patients present with bloody diarrhea, urgency, abdominal pain and tenesmus[2]. Recent studies depict an increasing prevalence of UC, with an estimated 5 million cases globally[5]. In the United States, the epidemiological burden of UC is comparable with global trends, with an incidence and prevalence of 6.3 per 100000 and 378 per 100000 people, respectively[6]. Underlying long-term inflammation alters colonic anatomy and functionality, thus predisposing patients to several downstream sequelae. This subsequently impairs quality of life and increases the risk of disability and colorectal cancer (CRC)[7]. In addition to the significantly increasing disease burden, the progressive and debilitating nature of UC results in a significant economic burden owing to increased direct and indirect costs associated with health care utilization[8]. Pharmacoeconomic data from the Crohn's and Colitis Foundation of America estimated that the annual economic costs are between US\$14.6 and US\$31.6 billion[9].

In contrast to its counterpart Crohn's disease, UC has not been considered a progressive disease[10]. This perception has been rightly altered with the availability of evidence that suggests otherwise[10]. Proximal disease progression is observed in approximately 50% of patients with limited UC at diagnosis[10]. The risk of progression increases with disease duration, notably at 15%, 30% and 50% at 5 years, 10 years and 25 years, respectively[10-12]. An aggressive disease course can lead to colectomy in 10%-15% of patients[12]. Furthermore, disease progression predisposes patients to greater needs for biologics, as well as greater risk for extraintestinal manifestations, pseudopolyposis, anorectal dysfunction, gut dysmotility, surgeries and hospitalizations[13-15].

Due to the availability of only less potent drugs, the natural disease course has not been fully elucidated. Over the past few decades, advancements in murine modeling systems have yielded novel mechanisms of disease onset and progression[16]. This has fueled identification of a wide array of molecular targets, resulting in a rapidly expanding therapeutic armamentarium. The introduction of tumor necrosis factor inhibitors in 2005 set the tone for utilizing advanced therapies in UC[17]. However, their use is complicated by the abundance of serious adverse events, suboptimal response rates and loss of response[18]. Modern biologics and small molecules, such as anti-interleukins, anti-integrins, sphingosine-1-phosphate modulators, and Janus kinase inhibitors (JAKis), provide a cost-effective means of targeting natural disease history[19]. No significant difference in overall safety outcomes was observed between UC patients receiving JAKis and patients receiving other active treatments[20]. Therefore, the safety of JAKis can also be debated. The availability of myriad therapies has shifted therapeutic goals from symptomatic resolution to well-defined objective end points, clinical remission, endoscopic remission and mucosal healing[21,22].

Disease status ascertainment based on clinical and endoscopic outcomes is inadequate. To date, despite the availability of adequate evidence, the utility of histological healing remains limited[21,22]. Emerging evidence supports the impact of attaining simultaneous clinical, endoscopic and histological remission on disease outcomes. Herein, we discuss the emerging concept of disease clearance (DC) and the currently available evidence with a view to expanding its applicability in prospective high-profile research and its transition to clinical utility.

TREAT TO TARGET: CURRENT GUIDELINES

DC incorporates components of target indices proposed in the selecting therapeutic targets in inflammatory bowel disease (STRIDE) program guidelines[21,22]. To better grasp the reasoning for DC, it is imperative to review current therapeutic target recommendations for UC. In 2015, the STRIDE committee added a new dimension to treatment aspirations with the introduction of treat-to-target (T2T) therapy[21]. Prior to the T2T concept, the primary aim of therapy was to achieve steroid-free disease remission based on the absence or presence of clinical symptoms[21]. However, this approach fails to alter disease progression or prevent long-term disease sequelae[21,23,24]. In recent decades, promising data have supported the use of more objective endpoints in clinical practice and trials. Achieving endoscopic remission or

mucosal healing was associated with improved long-term outcomes, such as steroid-free clinical remission; lower steroid utilization; and reduced rates of colectomy, dysplasia, CRC, disease relapse and hospitalization[21,25-30]. This finding supported the paradigm shift of treating beyond symptoms with a view to preventing structural damage and disability [21]. Furthermore, evidence of the effectiveness of T2T in treating other conditions, such as rheumatoid arthritis, diabetes and hypertension, supports its use in treating IBD[21,31-33]. Therapeutic adjustments were proposed on the basis of the achievement of predefined treatment goals with the aim of attenuating disease pathophysiology[21,34]. Subsequently, the importance of endoscopic assessment was outlined in the STRIDE[21]. Thus, the T2T strategy recommends the incorporation of a composite measure to ascertain disease status based on clinical remission/patient-reported outcomes (PROs) and endoscopic remission[21]. Clinical remission was defined as the resolution of rectal bleeding (RB) and normalization of stool frequency (SF)[21]. Clinical symptoms must be monitored every 3 months[21]. After adequate symptomatic control was achieved, follow-up every 6 months was considered adequate[21]. Endoscopic remission was defined as a Mayo endoscopic subscore of 0 or 1[21]. Endoscopic assessments were warranted every 3-6 months after the initiation of therapy[21]. When endoscopic evaluation is limited, resolution of inflammation should be ruled out by cross-sectional imaging[21]. A lack of evidence prevents the incorporation of histologic targets[21]. Finally, inflammatory biomarkers such as C-reactive protein (CRP) and fecal calprotectin (FC) were identified as adjunctive measures of inflammation rather than treatment targets[21].

Accumulating evidence and advancements in diagnostic modalities led to updated STRIDE guidelines[22,35]. In 2021, the STRIDE 2 guidelines incorporated time-dependent objective treatment targets ranging from short-term, intermediate-term and long-term goals of care[22]. The short-term target ensures that patients achieve a symptomatic response[21]. Intermediate goals include symptomatic remission, normalization of CRP levels and a decrease in FC to an acceptable range[21]. Approximately 15%-30% of patients fail to achieve a CRP response[36]. Therefore, the use of FC is preferred in biomarker assessments of inflammation[36]. The long-term treatment goals were endoscopic healing, normalization of quality of life and lack of disability[21]. Owing to superior disease outcomes, the endoscopic healing criteria were more stringent, with a Mayo endoscopic subscore of 0[22,30]. The low cost, ease of collection and lack of data from randomized controlled trials (RCTs) have led to treatment optimization driven by inflammatory biomarkers (CRP and FC)[22,37,38]. Despite the availability of evidence supporting the strong association of histologic healing (HH) with endoscopic healing and as a predictor of long-term outcomes, HH was endorsed only as an adjunctive target[22].

DC IN UC

What is DC?

DC is a novel emerging concept that has been adapted from dermatology[39]. DC is a composite measure defined as deep and comprehensive remission[40]. It encompasses the simultaneous attainment of clinical, endoscopic and histologic remission[40]. As a composite outcome, it holds the potential to improve treatment efficacy by increasing event rates and assessing all factors impacting disease activity[40]. Utilization of DC in psoriasis patients has yielded significant improvements in quality of life and disease control[41,42]. While it may represent the ultimate therapeutic target for psoriasis, DC was achieved in only 35.3% of patients[42]. DC has also demonstrated use in aiding therapeutic positioning in biologic drug efficacy comparator trials[43]. To avoid confusion in patients, DC should not be used synonymously with the term "cure".

Why incorporate DC in UC?

Current treatment goals devised by STRIDE committee utilize these endpoints individually at several predetermined targeted time points[21,22]. STRIDE 2 proposes focusing on the short to long term in a T2T manner[22]. Several discrepancies exist indicating that our current definition of disease remission is subpar. Despite achieving endoscopic healing, persistent RB and increased SF can be observed in 39% and 24%, respectively, of patients[44]. A subset of these persistent symptoms can be attributed to functional disorders, with irritable bowel syndrome being the most prevalent[45-48]. Chronic inflammation alters colonic physiology and anatomical integrity, resulting in abnormal colonic motility, a reduction in goblet cells, aberrant barrier function and sequelae of intestinal fibrosis[49-52]. The extent and location of these changes contribute to persistent PROs despite adequate disease control[44,53,54]. This increases therapeutic risks due to aggressive treatment strategies and unnecessary changes in therapy. On the other hand, there remains a risk of underlying endoscopic disease in 20%-50% of patients attaining symptomatic remission[44,55-57]. Therefore, the assessment of clinically asymptomatic patients must be supplemented by other objective measures of inflammation. Patients in clinical remission are less likely to seek medical attention, thus increasing their risk of developing sequelae related to unchecked smoldering inflammation[58]. Despite the use of modern therapeutics, 10%-30% of patients still require proctocolectomy for medically refractory disease[59,60]. The absolute risk of colectomy increases with each subsequent switch in therapy[60]. While response rates vary across drug classes, 30%-40% of patients fail to respond to initial therapy[61]. Patients primed with prior biologic exposure exhibit a stepwise reduction in response to subsequent therapies[61]. However, remission rates remain suboptimal, with 20%-30% of patients achieving disease remission in UC induction trials, indicating a perceived therapeutic ceiling[17,62-70].

The persistence of histologic activity despite endoscopic inactivity has been shown to increase the risk of disease progression, relapse and complications[71-73]. A discordance between histologic activity and quiescent macroscopic activity has been reported in > 30% of cases[74]. Compared with mucosal healing, histologic activity has shown superior performance as an independent predictor of clinical course[74-76]. Histologic inflammation has also been deemed an independent risk factor for the development of CRC[7]. A 3- to 5-fold increase in the risk for CRC has been observed in

patients with persistent histological activity[72]. The severity of histologic inflammation correlates with progression to advanced neoplasia[72]. Reversal of histologic disease has been shown to reduce the risk for CRC[77]. Achieving composite histologic and endoscopic improvement and remission correlate with PRO and reduced disability[78,79]. Despite being achievable in 55% of patients and growing evidence, histologic remission has not been formally designated as a therapeutic target[21,22,75]. In the majority of RCTs and regulatory trials, histological outcomes have been positioned as an exploratory or additional endpoint rather than a mandatory endpoint. Furthermore, the availability of multiple validated histological scoring systems, uniform endoscopic disease distribution and excellent predictive ability of inflammatory biomarkers for HH will facilitate the application of DC as a therapeutic outcome in UC[80-82]. This has given rise to the concept of deeper disease control by incorporating histologic activity as a mandatory endpoint. The data here support the hypothesis of total deep remission when combined with clinical, endoscopic and histological outcomes.

Consensus definitions of DC by the International Organization for the Study of IBD

In 2023, the first ever standardized guidelines defining DC were published by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD)[40]. It is expected that these guidelines will help standardize its use. Acknowledgment of the prognostic importance of histologic outcomes led to its incorporation as an official therapeutic endpoint[40]. The definition finalized by the IOIBD includes clinical, histologic and endoscopic remission of disease[40]. This culminates in all major time-dependent objective measures proposed in STRIDE 2. The expert consensus further delved deep to closely define each desired therapeutic target in line with the best available evidence. Clinical remission was defined as the total absence of clinical symptoms with a partial Mayo score of 0[40]. A Mayo endoscopic score of 0 and a Nancy histologic score of 0 define endoscopic remission and histologic remission, respectively[40].

Evidence supporting DC in UC as a therapeutic target

In a multicenter retrospective study, D'Amico *et al*[83] evaluated the impact of DC on long-term outcomes in UC patients. DC was defined as simultaneous clinical (partial Mayo score ≤ 2), endoscopic (Mayo endoscopic score 0) or histological remission (Nancy index 0)[83]. Adult UC patients with an endohistological evaluation within 16 wk postinduction and at least 12 months of follow-up were included. The median follow-up time was 24 months[83]. Of the 494 patients in the study, 109 (22%) achieved DC[83]. Patients who achieved DC had shorter disease durations (5 years *vs* 9 years, $P < 0.001$) [83]. Significantly lower rates of negative outcomes such as hospitalization (5.5% *vs* 23.1%, $P < 0.001$) and surgery (1.8% *vs* 10.9%, $P = 0.003$) were noted in patients who underwent DC[83]. When reanalyzed using more stringent criteria (Mayo endoscopic score 0, Nancy index 0, normal SF and absence of RB), 19.8% of the patients met the criteria for DC[83]. The rates of hospitalization (22.7% *vs* 5.1%, $P = 0.003$) and surgery (10.9% *vs* 1.0%, $P = 0.012$) were greater in patients without DC[83]. Taken together, attaining DC within 16 wk posttherapeutic induction significantly lowers health care expenditure, the risk of hospitalization and surgery (Figure 1). This underlines the importance of initiating early treatment. Furthermore, this finding indicates the need for developing more efficient drugs[84].

Andronic and Toader[85] conducted an analysis of 79 UC patients[85]. For the purposes of this study, DC was defined as clinical (partial Mayo score ≤ 2), endoscopic (endoscopic Mayo score ≤ 1) or histologic remission (nancy index 0)[85]. At the initial time points, patients were divided into two subgroups. Groups 1 and 2 were deemed to have DC ($n = 35$) and without DC ($n = 44$), respectively[85]. Patients in both groups were followed for 12 months. Patients who achieved DC (Group 1) did not experience disease complications or required surgery (0% *vs* 31.8%, $P = 0.03$, OR = 23.1)[85]. The rate of hospitalization was significantly lower in Group 1 than in Group 2 (8.57% *vs* 54.54%, $P = 0.002$, OR = 0.57, RR = 0.224)[85].

Nascimento *et al*[86] conducted a retrospective analysis of 56 patients with UC and DC at baseline[86]. DC was defined as clinical (partial Mayo score ≤ 2), endoscopic (endoscopic Mayo score ≤ 1) or histologic remission (chronic inactive/quiescent colitis)[86]. During the 3-year follow-up, none of the patients with DC required surgery, and only one was hospitalized[86]. The overall probability of maintaining remission was 76% at 3 years[86].

A natural question arises whether the achievement of such a stringent endpoint is possible. Kruis *et al*[87] conducted a post hoc analysis of 4 phase 3 clinical trials[87]. The data were pooled from 860 UC patients to determine the percentage of DCs induced by different doses of mesalazine[87]. Overall, 20% achieved DC, 13% received 1.5 g/day, 21.8% received 3 g/day and 18.9% received 4.5 g/day[87]. Furthermore, the rates of DC were consistent across disease activities in a dose-dependent manner[87]. According to a post hoc analysis of the VARSITY comparator trial, at week 52, DC was noted in a greater percentage of patients receiving vedolizumab than in those receiving adalimumab (29.2% *vs* 16.3%)[88]. The data here suggest that DC is an achievable target in clinical practice, for which the likelihood of reaching this stringent outcome is 20%-29%.

FUTURE AVENUES AND UTILITY IN CLINICAL LANDSCAPE

While still in its infancy, it is expected that the definition of DC will evolve to include ongoing or upcoming results[40]. Emerging evidence supports the correlation of rectal muscle remodeling (rectal compliance) with histologic normalization and impact on quality of life[89]. Newer measures of quality of life, such as fecal urgency, are also under investigation [40]. Future avenues must assess superiority with differences in long-term outcomes with DC *vs* histological remission alone. Currently, the ongoing VERDICT trial aims to determine whether DC alone is superior to steroid-free symptomatic remission or steroid-free endoscopic remission combined with clinical remission[90]. To aid in the transition to routine clinical care, DC should be considered a secondary endpoint in RCTs[40]. Current evidence of DC is mainly driven by retrospective and post hoc analyses. Most current studies were conducted prior to the release of standardized DC guidelines. Therefore, some studies utilize different definitions of clinical remission. To accurately assess the impact of

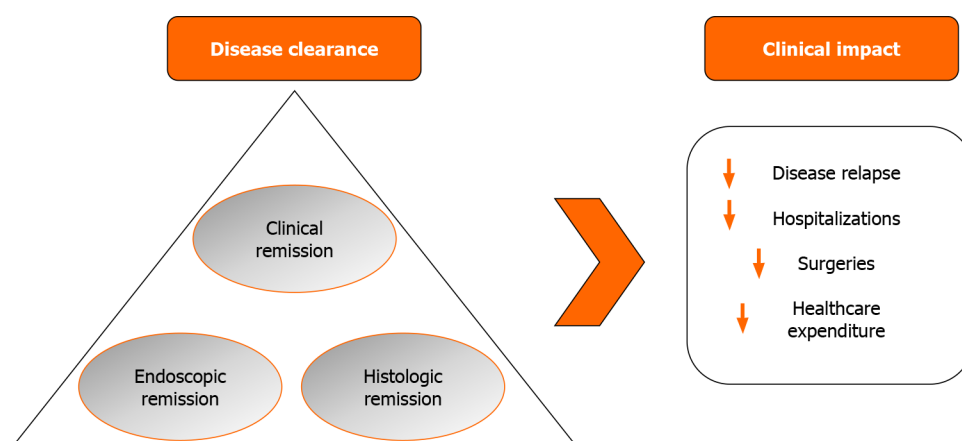


Figure 1 Defining disease clearance in ulcerative colitis and its perceived impact on clinical outcomes.

achieving DC on long-term outcomes, future studies must incorporate a uniform definition of DC. In addition, additional prospective studies with predefined objectives must be conducted. While patients who achieved DC were shown to have a lower baseline inflammatory burden, future studies must assess the role of inflammatory biomarkers. Given that achieving DC might be considered a difficult task, developing predictors of DC is important. The likelihood of achieving DC may be increased by dual therapy and by discovering biomarkers of drug response. Evidence pertaining to the value of dual therapy remains limited, with few prospective large-scale studies conducted to date[91]. Therefore, the role of dual therapy in inducing DC remains unknown. The impact of DC on dire sequelae such as dysplasia and CRC must also be ascertained. Transcriptional signatures specific to disease remission have also been delineated[40]. These include increased expression of genes regulating o-glycosylation and GAP junction trafficking and decreased expression of toll-like receptors[40,92]. This paves the way for the addition of molecular remission as an endpoint in DC with a direction for developing reliable molecular predictors of disease outcomes.

CONCLUSION

DC is a novel therapeutic outcome in UC patients and has the potential to provide superior disease control and reduce the risk of long-term complications. Prospective studies are necessary to ascertain the cost effectiveness, risk-benefit ratio and impact on long-term outcomes.

FOOTNOTES

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