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REVIEW OF CURRENT AND FUTURE TREATMENT FOR ULCERATIVE COLITIS

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ABSTRACT

For ulcerative colitis (UC), the STRIDE initiative in 2015 recommended changing the therapeutic focus to modify the illness's natural history by periodically monitoring objective assessments of disease activity and then customising therapy appropriately. UC is an inflammatory bowel disease (IBD). The paradigm shift in therapeutics has been widely referenced in the scientific community. Since the STRIDE recommendations were published, additional research on the most effective UC therapy targets has continued to gather. Treat-to-target techniques in clinical practise for UC are discussed, as are the hurdles to their implementation, in this systematic review that reviews the data accumulated since the STRIDE UC guidelines. It also offers future research areas.

Keywords: ulcerative colitis, PubMed, UCEIS, STRIDE

I. Introduction

In people with ulcerative colitis (UC), a chronic disorder, inflammation in the colon can progress from mild to severe, resulting in frequent bloody bowel movements, colonic motility dysfunction, potential tissue destruction, and the need for surgical intervention. One-third of persons with mild UC will have the disease by the time the condition has advanced by ten years. Approximately 10 percent to 15 percent of patients with UC will require a colonoscopy at some point in their lives. In up to a third of patients, colectomy is associated with complications; consequently, establishing mucosal healing through treatment reduces the chance of needing to have a colonoscopy (Ashton, *et al.* 2019). By concentrating solely on symptoms in the treatment of UC, it is possible to leave untreated, smouldering sickness (i.e., unhealed mucosa), which increases the chance of recurrence of the disease. Despite improved treatment options, the number of colonoscopies performed has not reduced over the previous decade. This emphasises the need of developing novel treatment techniques.

A approach adapted from the paradigm for the treatment of rheumatoid arthritis, the T2T strategy attempts to achieve disease remission by altering therapy in response to the achievement (or failure to achieve) of established therapeutic response targets (Ashton, *et al.* 2019). As part of the STRIDE committee's proposed composite goal of normalisation of bowel habits and intestinal inflammation, histology and biomarker objectives were included, however there was insufficient evidence to warrant their inclusion, according to the committee.

II. Rationale

Evidence suggests that full mucosal healing in UC may be the best treatment objective. Aside from endoscopic healing, histological healing also has to be examined since data shows that microscopically active illness may

remain in macroscopically inactive disease (Sexton, *et al.* 2020). The T2T method in UC appears to be trailing due to the fact that many doctors continue to treat patients based on their symptoms.

III. Aim

The purpose of this study is to give a comprehensive overview of the existing research on T2T methods in UC, analyse hurdles to adoption, and offer practical guidance for their inclusion into clinical practise.

IV. Methods

On March 31, 2018, we conducted an electronic PubMed search to analyse the growing evidence for prospective therapeutic targets in clinical variables, patient-reported outcomes, endoscopy, histology and imaging, and biomarkers since the STRIDE systematic review.

They were almost identical to those used in the STRIDE article. These research included randomised clinical trials, interventional studies and observational studies as well as meta-analyses and reviews in the selection process (Sohail, *et al.* 2019). Cancer, neoplasm and dysplasia investigations were not included in this study.

V. Results

New IBD management criteria, particularly for UC, were recommended by STRIDE. There are some new findings that might assist refine some of the recommendations in this section to continue researching and enhancing UC therapies (Figure 1).

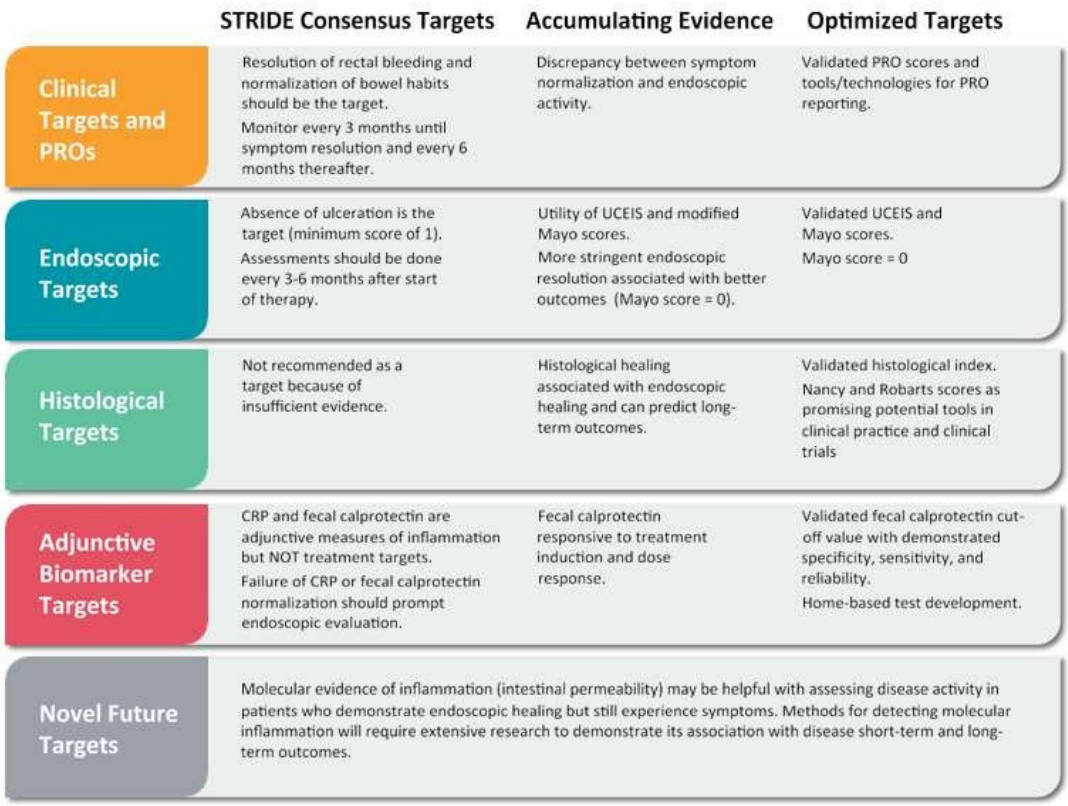

Figure 1. Accumulating evidence and evolution of specific targets in the management of UC. CRP, C-reactive protein; PRO, patient-reported outcomes; UCEIS, UC Endoscopic Index of Severity.

VI. Clinical perspective

It is required to demonstrate that the T2T approach may influence the course of the disease and prevent incapacity and long-term difficulties in order to justify the higher expenditures and healthcare consumption incurred (Sohail, *et al.* 2019). A long-term follow-up was necessary to evaluate the effect on disease course and support a paradigm shift in management, despite the CALM trial demonstrating that a strict control strategy might improve clinical and endoscopic results in CD. REACT2, which stands for Reactive Early Algorithm for Combination Therapy in the Treatment of Crohn's Disease, is another research project now under process.

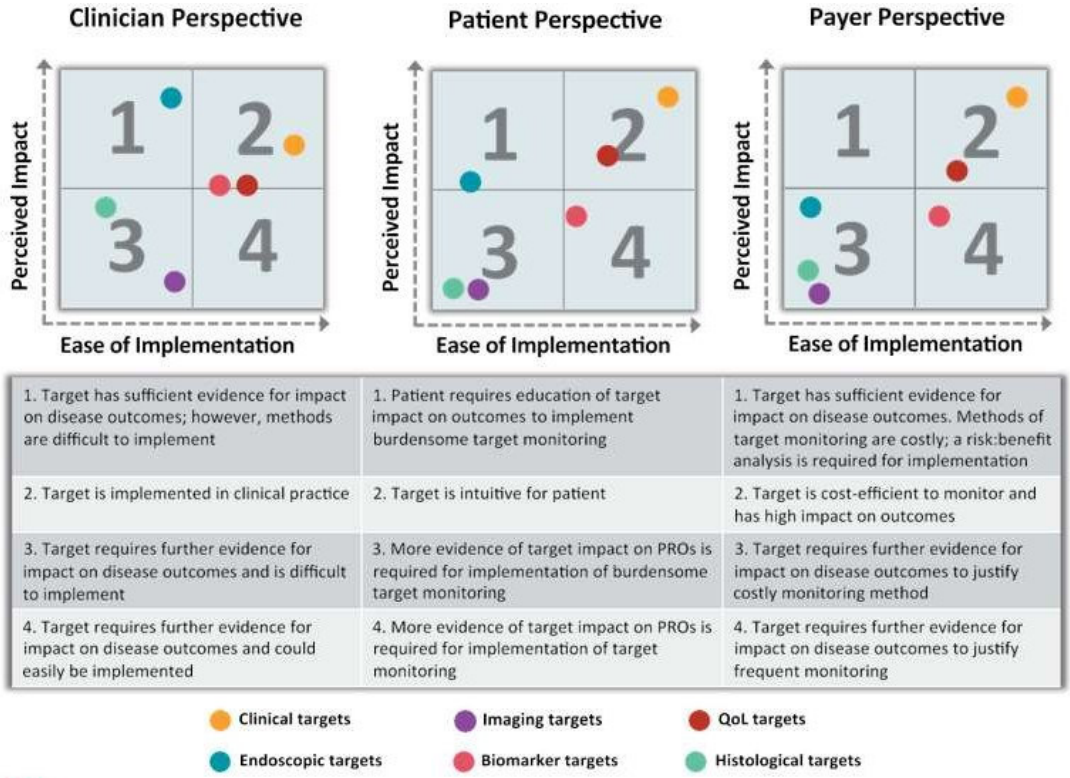

Figure 2. Feasibility of and barriers to implementation of a T2Tapproach. In the above matrices, the targets are placed on a scale that accounts for the ease of implementation as a treatment target (x-axis) and perceived impact of treatment target on disease outcome (y-axis). Quadrant 1 contains targets that are difficult to implement but have high perceived impact by stakeholder, quadrant 2 contains targets that are easy to implement and have high perceived impact, quadrant 3 contains targets that are difficult to implement and have low perceived impact, and finally quadrant 4 contains targets that are easy to implement and have low perceived impact. Each stakeholder will require different levels of evidence and education to successfully adopt the treat-to-target approach proposed by the STRIDE committee. Barriers to implementation are summarized under each matrix. PRO, patient-reported outcomes; QoL, quality of life; T2T, treat-to-target; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease.

Following the findings of this research, we devised an algorithm for incorporating T2T approaches into therapeutic therapy for urological cancer patients (Figure 3) (Zhang, & Merlin, 2018). Any algorithm would need to be evaluated in a clinical study before it could be demonstrated that it improved health outcomes and quality of life for the participants involved.

With relation to the evaluation of healing after endoscopic surgery, there is a paucity of evidence linking the pursuit of endoscopic goals to improved long-term outcomes. It is demonstrated in this review that there are significant differences between the two methods of calculating the dis- ease score (Sohail, *et al.* 2019). As shown in Figure 3, both Mayo and UCEIS can be used in conjunction with one another. However, Mayo may be more familiar and hence more practical in clinical practise than UCEIS, which is our ideal score (for both, the target would be a score of 0). In order to close current disparities, prioritising consistent adoption and recording of disease ratings in patient reports would be a crucial first step to address such discrepancies. If at all possible, this

should be initiated at Mayo Clinic with the objective of eventually incorporating UCEIS into the clinic's standard of care.

There is a lag between the incorporation of histology scores and their publication. As shown in Figure 3, an algorithm for integrating histologic evaluation into routine practise could be developed; however, histologic score targets are not recommended for current practise due to a lack of prospective interventional studies demonstrating the benefit of solely histologically guided therapy decisions (Bertani, *et al.* 2020). If there are no other choices available, it is not recommended to terminate therapy in patients who have endoscopic remission and histologic inflammation until prospective data on this topic become available.

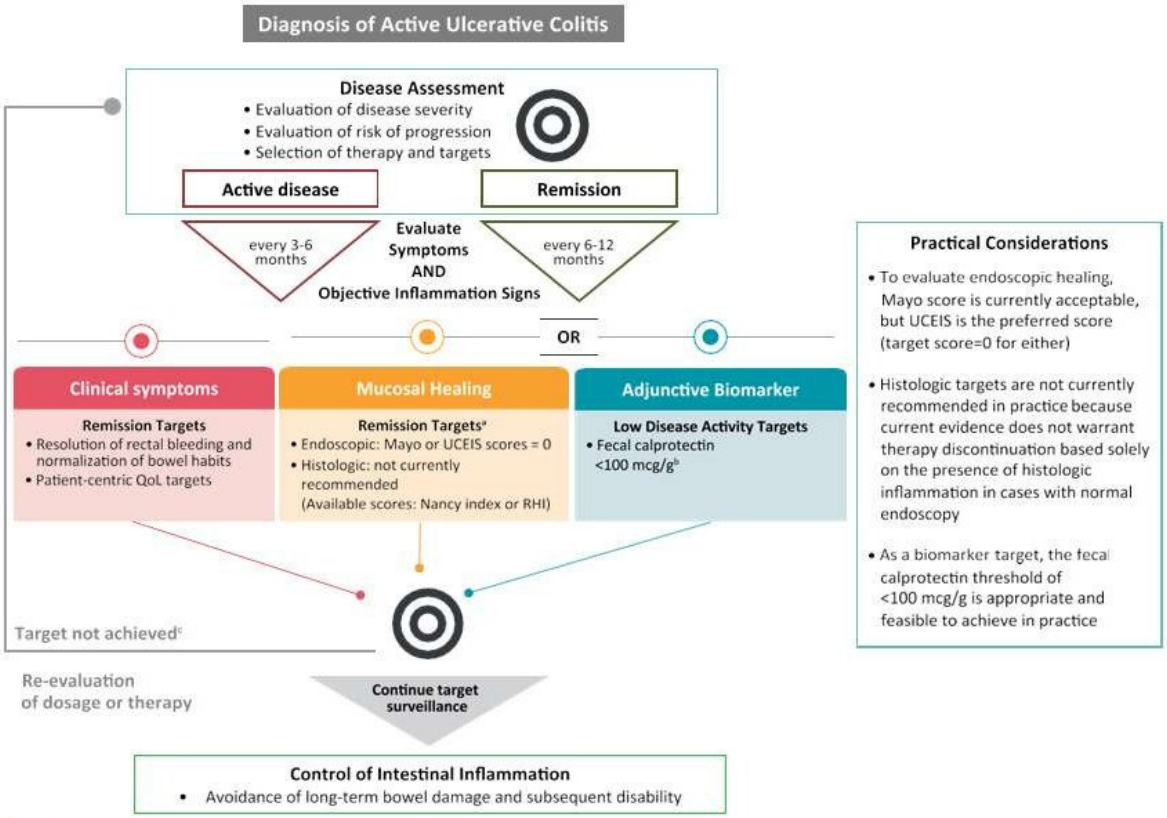

Figure 3. Proposed ulcerative colitis T2T algorithm. [a]Mucosal healing as a treatment target must involve patient decision because of the high burden of monitoring and potential need for therapy escalation despite symptom resolution. [b]Biomarker normalization as a treatment target must involve patient decision because of potential need for therapy escalation despite symptom resolution. [c]If adjunctive biomarkers are not improving or normalizing, mucosal healing targets should be reassessed. QoL, quality of life; RHI, Robarts Histopathology Index; T2T, treat-to-target; UCEIS, UC Endoscopic Index of Severity.

Another obstacle to the widespread use of endoscopic or histologic evaluations is a lack of standardisation in clinical practise of endoscopic grading (Card, *et al.* 2018). Non-invasive monitoring technologies have been shown to be beneficial in the prediction of relapse in patients with UC, however this is an area that is currently lacking in data-driven evidence to support the use of these tools to minimise healthcare and patient burden. Current research shows that it can be used in clinics for disease monitoring as the most advanced noninvasive method. Because clinical investigations have utilised varied thresholds (13.9–261 mg/g) and correlated measurements (e.g., reference data, definition of relapse), it is still being investigated whether a well-validated FC threshold can be used to signal mucosal healing. In terms of current practise, we recommend that a cutoff point of 100 mg/g may be used to indicate modest disease activity when it comes to FC testing (Figure 3). In order to "benchmark"

the FC level for each patient, it is recommended that FC be measured as near as possible to the time of an endoscopic examination (Sankar, *et al.* 2021). There have also been trials on home-based testing that let patients to take their own measurements, which may assist achieve regular FC monitoring with reduced patient load. Imaging modalities can be used to monitor disease activity in a non-invasive manner (Sankar, *et al.* 2021). Long-term problems can be exacerbated in individuals at increased risk of endoscopic illness and structural alterations as a result of persistent inflammation. Research on the specificity, sensitivity and reliability of these instruments is still needed.

The PROs (rectal bleeding and stool frequency) have emerged as two essential criteria for UC, but other QoL domains (e.g. weariness, impairment) have been poorly investigated and are not unified into a single instrument (Ungaro, *et al.* 2019). Increased regulatory interest in PROs might and should lead to the validation of tools following regulatory criteria for medication development in IBD.

VII. Payer perspective

Payers will require clear and unequivocal assessments of the favourable risk-benefit ratio for T2T procedures as compared to the current status quo before T2T techniques can be widely used. It would be ideal if these decisions were made on the basis of long-term randomised controlled trials and cost-effectiveness studies (Niu, *et al.* 2021). The use of early aggressive therapy (or alternatively, a more fast step-up technique) and regular monitoring may prove to be more cost-effective in the long run, despite the fact that the initial costs are higher. Reduced expenses and problems connected with monitoring are certain to make the adoption process a little less challenging.

VIII. Patient perspective

Because motivated individuals would be expected to follow and adhere to protocols even during periods of sickness remission and symptom resolution, patient considerations may be critical to the success of personalised T2T techniques, particularly in the context of chronic illness. In order to achieve their unique aims and gauge their level of satisfaction with the treatment's target, physicians should consult with their patients. Patients who wish to achieve deeper healing or remission (either histologically or molecularly/biomarker-based) must be willing to endure dose escalation in order to adhere to a T2T regimen (Zhang, & Merlin, 2018). Considering the severity of the ailment as well as the patient's tolerance for strong therapy and, maybe, recurring procedures and tests, while developing a personalised treatment strategy, is critical. To the greatest extent possible, patient education should also encourage the adoption of lifestyle modifications (dietary recommendations, for example), which may have poor intrinsic effectiveness but may aid in symptom relief.

T2T strategies have the ultimate objective of dramatically altering the course of UC, enhancing quality of life, and reducing the likelihood of severe and debilitating long-term functional impairments or disabilities in the longrun (Niu, *et al.* 2021). To ensure that this clinical paradigm is validated and that it is widely implemented, it willbe necessary to evaluate how effectively T2T procedures function in connection to particular goals from a varietyof viewpoints. It will be essential to conduct studies with a broad scope (including assessments of clinical status, surgery rates, resource consumption, and cost-effectiveness), a large sample size, and a long duration in order to validate these findings. For these types of studies, real-world cohorts could be a good starting point; however, it is important not to underestimate the difficulties of defining appropriate treatment goals and outcome measures, and of conceptualising comparative schemas (for example, who would serve as the study's reference controls)

(Danese, *et al.* 2019). It is possible that a big prospective clinical study in UC, such as that of CALM or REACT2 in CD, may be beneficial if a T2T approach in CD can aid clinicians in appreciating the value and feasibility of achieving targets using existing medications and monitoring technology.

IX. Conclusion

Increasing our understanding of intestinal inflammation may pave the way for the development of innovative treatment alternatives in the future. Using endomicroscopy research, researchers have been able to generate more precise mucosal healing criteria (including crypt numbers, crypt lumen deformity, crypt lumen leakage, and vascular leakage) (Danese, *et al.* 2019). According to the findings of further study, endomicroscopic mucosal abnormalities may be able to predict future clinical outcomes. Biomarker research is a dynamic field that is continually expanding. Several gene transcripts that reacted to anti-tumor necrosis factor treatment and were associated to endoscopic activity of the illness were discovered in a recent research; these molecular indicators identify changes in disease activity with more accuracy than CRP, ESR, and platelet count (Bertani, *et al.* 2020). It is still unclear why some persons who have experienced endoscopic remission continue to endure chronic symptoms in the absence of further study. A key study and management tool would be the development of an indicator that goes beyond endoscopic or histological scoring (akin to the Le'mann score in CD).

The T2T paradigm is gaining traction in IBD after being broadly recognised in rheumatoid arthritis (Ungaro, *et al.* 2019). A increasing body of data points to its value in the treatment of both CD and UC. The T2T guidelines (STRIDE) might be revised for both CD and UC based on the new research (Sexton, *et al.* 2020). A closer look at the disease's underlying mechanisms may lead us to identify the importance of fibrosis and molecular repair. All of these aspects may be crucial in preventing functional deficits and impairment in UC over the long run.

We cannot dispute that incorporating T2T approaches into everyday practise continues to be a struggle and necessitates a paradigm change. It is necessary to redouble efforts in evidence generation to validate reliable, preferably non-invasive endpoints that predict favourable long-term outcomes, as well as establishing that a T2T strategy is superior in terms of risk-benefit and cost-effectiveness to current paradigms, in order to achieve truly personalised treatment plans and goals for patients.

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