Treat-to-Target: The Era of Targeted Immunosuppressive Agents in IBD Management

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ABSTRACT

With the advent of biologic agents, the treatment of patients with Inflammatory Bowel Diseases (IBD) has changed from managing symptoms to achieving remission of disease. Disease remission is associated with better outcomes than symptomatic care alone. The Treat-to-Target paradigm provides targets that serve as surrogates for achieving disease remission. The most important target is endoscopic mucosal healing and other targets include symptomatic response, symptomatic remission, biomarker normalization, and normalization of patient's quality of life. Targets are reached via utilization of biologic medications that may be modified or substituted as goals are not met. IBD Qorus represents a national collaborative of academic IBD centers and private gastroenterology practices using the Treat-to-Target approach and patient-centered communication methods to provide better care for all patient's suffering from IBD.

KEYWORDS: IBD; Crohn's Disease; Ulcerative Colitis; Treat-to-Target; QORUS

Management of patients with Inflammatory Bowel Disease (IBD) underwent a paradigm shift from managing symptoms to a focus on achieving remission, also known as the Treat-to-Target (TTT) approach. TTT was borrowed from rheumatologists and adopted by gastroenterologists to focus on achieving remission of IBD as defined by surrogate markers, chief among them is mucosal healing, and creating goals (targets) that physicians and patients could work together to achieve. This guidance was proposed in the Selecting Therapeutic Targets in IBD program, STRIDE and STRIDE II initiatives by the International Organization for the Study of IBD via systemic review and expert consensus.[1,2] This method replaces older strategies that focused primarily on controlling symptoms which have not proven to be effective in altering a patient's disease course. The main goal, or treatment target, of TTT is endoscopic mucosal healing and other targets that are also regularly monitored, which include symptomatic response, inflammatory biomarkers, and overall patient well-being.

Treat-to-Target utilizes the principle that a symptomatic response to treatment does not always result in a decrease in mucosal inflammation[3]; ongoing inflammation may result in complications of IBD such as neoplasia, abscess, and strictures. Mucosal inflammation is quantified endoscopically by mucosal healing, the gold standard outcome for all IBD treatment modalities, as mucosal healing predicts sustained clinical remission and resection-free patient survival.[4] The CALM trial showed that treatment escalation of biologic therapy via symptoms alone led to less mucosal healing when compared to objective measurements, thus providing the foundation for the TTT approach.[5] Furthermore, because assessment of mucosal healing via endoscopy is invasive and expensive, other objective therapeutic targets were needed so surrogate markers of inflammation such as laboratory data were included as targets.

For primary care providers, TTT is likened to monitoring patients with diabetes' hemoglobin A1c every three to six months and using various tools such as insulin and insulin secretagogues to achieve the goal <7%. While microvascular damage to kidneys, eyes, and peripheral nerves may be present in patients with A1c >7%, they are often asymptomatic. Similarly for patients with IBD, significantly active inflammation may be present while the patient is clinically asymptomatic, thus clinicians should consider changing therapies to achieve treatment targets.

For patients, TTT can be likened to car maintenance. While the check engine light may not be on, and the car is seemingly running smoothly, there still may be hidden problems. By having yearly visits with diagnostic maintenance tests, drivers can determine if there is any significant damage occurring to the car and attempt any measures to alleviate or stop the damage.

The goals for the TTT are achieved primarily through biologic medications, small molecule inhibitors, aminosalicylic acid agents, and immunomodulators in both ulcerative colitis (UC) and Crohn's Disease (CD). **Table 1** shows medications that are commonly used in achieving these targets. Generally, these medications are started at the lowest effective dose and up titrated as needed to achieve TTT goals. Another biologic was approved for Crohn's in late June, 2022: Rizankinumab, a monoclonal antibody targeting IL-23. Several other anti-IL23 inhibitors will become available in the next few years. **Table 2** shows a general timeline for achieving the specific targets as defined by the STRIDE-II team.[2]

Table 1. Common Medications used in the treatment of IBD

Generic Name	Trade Name(s)	Disease Treated	Major Side Effects	Clinical Pearls
Anti-tumor necrosis factor agents				
Infliximab	Remicade, Inflectra, Renflexis, Ixifi, Avsola	CD and UC	Increased risk of bacterial and atypical infections, possibly lymphomas and non-melanoma skin cancer, and worsening congestive heart failure.	Contraindicated in patients with NYHA Class III or IV heart failure
Adalimumab	Humira, Amjevita, Cyltezo	CD and UC		
Golimumab	Simponi	UC		
Certolizumab	Cimzia	CD		
Anti-Integrin Inhibitors				
Vedolizumab	Entyvio	CD and UC	No significant increased risk of infections.	Increased risk of Progressive Multi-focal Leukoencephalopathy if infected with JC virus (Natalizumab only).
Natalizumab	Tysabri	CD		
Interleukin-12/23 Inhibitors				
Ustekinumab	Stelara	CD and UC	Increased risk of infection and possibly non-melanoma skin cancer	
5-Aminosalicylic Agents				
Mesalamine	Asacol, Pentasa, Delzicol, Lialda	CD and UC	Allergic reactions, paradoxical diarrhea, and pancreatitis.	
Antimetabolites				
6MP/Azathioprine		CD and UC	Bone marrow suppression, hepatotoxicity, pancreatitis, lymphoma	Test for Thiopurine Methyltransferase before use to prevent severe bone marrow aplasia
Jak Inhibitors				
Tofacitinib	Xeljanz	UC	Increased risk of infection, lymphoma, thrombosis, and cardiac events	
Upadacitinib	Rinvoq	UC	Increased risk of infection, theoretical risk of perforation	
Sphingosine 1 Phosphate Receptor Modulator				
Ozanimod	Zeposia	UC	Dose dependent decreases in heart rate, increased risk hypertension, associated with increased risk hepatotoxicity, increased risk of infection	

Table 2. Summary of Short-Term, Intermediate, and Long-Term Targets

Short-Term (within 3 months)	Intermediate Targets (within 6 months)	Long-Term targets (6–9 months)
1. Symptomatic response - CD=50% reduction in PRO2 abdominal pain and stool frequency - UC=50% reduction in PRO2 rectal bleeding and stool frequency	1. Symptomatic remission - CD=50% reduction in PRO2 abdominal pain </=1 and stool frequency </= 3 - UC= PRO2 rectal bleeding score of 0 and stool frequency of 0 2. Normalization of biomarkers - Fecal calprotectin generally preferred over CRP	1. Endoscopic Healing - Endoscopic remission is preferred 2. Normalized Quality of Life

TREATMENT TARGETS

While not the most important marker for disease progression, symptomatic response is an important patient-centric target for both physicians and patients in the management of IBD. Patients often value symptomatic response above other targets, while mucosal inflammation leading to long-term problems may still be present despite clinical remission. The REACT trial showed that treating to a target of clinical remission generally results in lower rates of surgery, hospitalization, and disease-related complications.[6] The patient-reported outcomes (PRO2) score quantifies and standardizes symptoms of IBD and includes daily stool frequency and abdominal pain for CD and normal stool frequency and absence of rectal bleeding for

Table 3. Simplified PRO2 Score for Crohn's Disease

	Day 1	Day 2	…	Day 7	Average	Weighing Factor	Total
# Liquid or Very Soft Stools						X2	
Abdominal Pain (3=severe, 2=moderate, 1=mild, 0=none)						X5	
						Pro2 Total=	

Table 4. Simplified PRO2 Score for Ulcerative Colitis

Perceived Stool Frequency	Normal=0	1-2 more stools than normal=1	3-4 more stools than normal=2	5+ more stools than normal=3
Perceived Severity of Rectal Bleeding	No blood=0	Streaks of blood for over half the time=1	Obvious blood=2	Blood passed without stool=3

UC (**Tables 3 and 4**). Symptomatic response is divided into clinical response, a short-term target, and clinical remission, an intermediate target. Clinical response for CD is defined as a 50% reduction in PRO2 abdominal pain and stool frequency and for UC a 50% reduction in PRO2 rectal bleeding and stool frequency by 50%. Clinical remission for CD is defined as PRO2 abdominal pain </=1 and stool frequency </= 3 and for UC a PRO2 rectal bleeding score of 0 and stool frequency of 0. If clinical response or remission cannot be achieved within 1–2 months for clinical response or 3–6 month for clinical remission, treatment modification should be considered. Given there is a closer correlation between symptomatic response and mucosal healing in UC compared with CD,[7] clinical response is considered a more important target in UC. In addition to symptomatic response, there is also a focus on steroid-free symptomatic remission, decrease in emergency department visits/hospitalization, and other patient-centered goals such as desire for pregnancy.

Endoscopic healing is the most important target in the TTT approach, which is generally defined as no macroscopic injury on direct mucosal imaging via colonoscopy. Mucosal inflammation is associated with poor long-term outcomes, including increased risk of bowel damage and other complications.[4,8] While endoscopic healing is considered a long-term goal, endoscopic response to treatment can be used to evaluate intermittent responsiveness to treatment in the short term. Generally, a significant decrease in inflammation on colonoscopy is considered endoscopic response, while near complete resolution of inflammation is considered healing. Colonoscopy should be considered six to nine months after starting therapy for CD and three to six months after starting therapy for UC. Sigmoidoscopy can take the place of colonoscopy for UC. Capsule endoscopy or balloon enteroscopy should be considered for CD depending on the anatomic disease location and phenotype.

Histologic healing is not currently a target in the TTT protocol. While histologic remission may result in fewer long-term complications and lower cancer risk in UC,[9] trying to achieve histologic remission has several drawbacks. Sample error can occur in CD depending on biopsy site, inter-reader reliability can vary among pathologists in both diseases, and most importantly, histologic remission is difficult to achieve with an estimated 10% of patients with CD[10] and 33% of patients with UC[11] achieving histologic response despite long-term treatment.

Cross sectional imaging is not a treatment target currently but is a useful adjunct in monitoring disease in IBD. For CD, imaging can find proximal lesions in the small bowel that are not seen on colonoscopy and determine full thickness healing, which may not always correlate with mucosal healing. Popular in Europe and other countries, point-of-care small bowel ultrasound may represent an efficient way to examine for CD or UC flare. Findings that are concerning include increased bowel wall thickness, increased blood flow to segments of bowel, bowel hypomobility, hypoechogenic bowel wall pattern, and lymphadenopathy.[12,13] Diagnosis of IBD associated complications such as strictures or fistulas with ultrasound and usage of contrast enhanced ultrasound and elastography represent future directions for managing IBD with ultrasound.

Fecal calprotectin (FC) and C-Reactive protein (CRP) are two important markers of inflammation for patients with IBD as they are objective, non-invasive, and inexpensive. Biomarkers are often obtained post induction, then every six to twelve months throughout the patient's disease. FC has been shown to predict clinical remission[14] and probability of relapse in patients with CD.[15] The goal for FC in patients with CD is variable, and generally levels greater than 150 ug/g are associated with inflammation. High CRP in patients with CD is associated with higher risk of relapse,[16] while normalization predicts long-term remission.[17] For UC, FC is more sensitive than CRP to predict endoscopic activity and is highly correlated with symptomatic and endoscopic disease.[18] Biomarkers like FC are important adjunctive markers of inflammation and in general correlate with endoscopic inflammation thus providing a noninvasive option. FC is more accurate for colonic inflammation compared with small bowel.[19] However, despite its better performance than CRP, it can have false negatives and/or positives.

To take a holistic approach to IBD care, quality of life and disability have been added as a long-term treatment target

for patients with IBD. While FC has moderate correlation with patient wellbeing,[20] earlier guidelines did not take patient's overall quality of life into account. Frequent assessments of patient's quality of life are now recommended to further elucidate what is important to the patient; thus, there should be a conscious effort to manage factors associated with poorer quality of life such as presence of a stoma, open instead of laparoscopic surgery, and mood disorders.[21–23] In situations where mucosal healing has been obtained, there are still opportunities for multidisciplinary care with psychiatry, psychology, physical therapy, and social workers in the pursuit of restoring an individual's quality of life and ensuring a reduction in disability.

IBD QORUS

IBD Qorus was developed by the Crohn's & Colitis Foundation to help develop a therapeutic alliance between patients, providers, and researchers to improve the care of patients with IBD. The mission of the Crohn's & Colitis Foundation is to, "…find a cure for Crohn's disease and Ulcerative Colitis while doing everything we can to improve the daily quality of life for patients with inflammatory bowel disease."[24] IBD Qorus is an electronic platform that allows for collaboration between enrolled gastroenterology clinics and patients. Rhode Island-based GI Associates has been an active participant in IBD Qorus for many years. After a patient consents to participate in IBD Qorus, they are sent a survey before their next appointment. This patient-centered survey was designed to briefly address individual's symptoms and goals, focusing on what is most important for the patient during their visit. This survey is reviewed by the provider prior to the visit and again during the visit with the patient. By taking the time to complete a survey prior to their visit, patients and providers both come to the visit with clear goals in mind, thus facilitating improved shared decision-making. The end goal of this process is to shift the focus of the appointment away from the disease and towards the patient's quality of life. The survey also prompts physicians to consider when they should next check for mucosal healing, either via labs or endoscopy, thus also targeting the TTT principles. Furthermore, deidentified data from the surveys populate a database that allows researchers to determine trends in population health.

IBD Qorus utilizes the Institute for Healthcare Improvement Breakthrough Series to achieve quality improvement that can then be widely disseminated. The Breakthrough Series model utilizes Plan-Do-Study-Act (PDSA) cycles after initial in-person learning sessions where promising best practices are widely distributed, and future directions are proposed. There are monthly calls with IBD Qorus staff where PDSA progress and challenges are discussed and addressed jointly.

The data from pre-appointment surveys and PDSA cycles have been used to improve care of IBD patients. For example, low-cost practice changes utilized in IBD Qorus have been shown to decrease unplanned healthcare utilization,[25] and decrease cost by an average of $2,528 per patient.[26] Clinical care pathways for nutritional care[27]and anemia management[28] have also been developed through IBD Qorus. Data is synthesized into reports and sent back to providers who can find clinic-wide trends in data compared with other sites, which can help guide future site directed PDSA cycles. With more than 50 sites nationally, best practices can be shared and benchmarking for important quality issues like steroid use and hospitalization can be examined.

CONCLUSION

The TTT approach represents a paradigm shift in improving the quality of care of IBD patients. The TTT approach focuses on endoscopic mucosal healing, inflammatory biomarkers, and overall patient well-being, and not just symptoms to keep IBD in remission. IBD Qorus is a growing network of patients and providers who use the TTT framework to share their experiences and data to further advance IBD care. Future studies are further evaluating clinical outcomes of changing biologic therapy in patients who are otherwise completely asymptomatic with active mucosal disease in efforts to further validate TTT.

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