ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Using a Treat-to-Target Approach to Manage Patients With Inflammatory Bowel Disease

Cynthia Seow, MBBS, MSc
Professor of Medicine
Division of Gastroenterology and Hepatology
Departments of Medicine and Community Health Sciences
University of Calgary
Calgary, Alberta, Canada

G&H What led to the concept of a treat-to-target approach for the management of patients with inflammatory bowel disease?

CS Traditional management approaches to inflammatory bowel disease (IBD) were hampered by the efficacy of the drugs that were available. These drugs, which included corticosteroids, were only able to achieve clinical outcomes (ie, provide symptom relief). Patients could feel better, but the drugs did not necessarily have the power to achieve deeper healing and keep patients well in the long term. As IBD physicians, we always knew there was a disconnect between symptoms, laboratory tests, and, most importantly, endoscopic evaluation. For example, if a patient was feeling well (symptomatic remission) but still had disease activity, as evidenced by blood or fecal tests, radiologic investigations, or endoscopy, it was only a matter of time before the patient had a disease flare and bowel damage occurred. With time, endoscopic healing not only became measurable but also achievable with new therapies. Importantly, we knew that deeper targets such as endoscopic healing were more likely to result in long-term remission.

The concept of treat-to-target was formalized by an initiative of the International Organization for the Study of Inflammatory Bowel Disease, with the first iteration of the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) guidelines published in 2015 and the second iteration published in 2021. With the treat-to-target approach for the management of IBD, physicians treat patients deeper to improve quality of life with the goal of avoiding flares, hospitalizations, and surgery. Physicians also aim to intervene early, at the stage of subclinical inflammation, before the patient becomes symptomatic, and hopefully change the natural history of the disease. With careful monitoring, physicians can be alerted if a current therapeutic strategy is not working and can optimize the existing therapy or change it to a more appropriate option in order to treat the patient to the appropriate target(s).

G&H What are the treatment targets for the short, medium, and long term in ulcerative colitis and Crohn's disease?

CS The short-term target (within the first 6 weeks of treatment) is ensuring that patients achieve a symptomatic response. This is reflected in a reduction in stool frequency and abdominal pain in patients with Crohn's disease, and a reduction in rectal bleeding in addition to a decrease in stool frequency in patients with ulcerative colitis. This early improvement in quality of life also serves as positive reinforcement, making it more likely that individuals will continue with their medication.

Medium-term outcomes involve symptomatic and biochemical remission. This includes a normalization of C-reactive protein (CRP). However, it must be recognized that 30% of patients do not necessarily mount a CRP response; therefore, the use of fecal calprotectin is preferred, as it is a very sensitive marker for inflammation. The aim is for fecal calprotectin to drop within the first 3 months of therapy. Further advantages of fecal calprotectin monitoring are that it is an excellent biomarker of subclinical inflammation and it can predict a flare in the next 3 to 6 months, allowing for actionable change.

Long-term targets (ie, 6-12 months into therapy) include radiologic/sonographic and, importantly, endoscopic parameters of healing. Ultrasonographic markers,

including bowel thickness, mesenteric fat involvement, vascularity, and reactive lymphadenopathy, reflect transmural involvement. For endoscopic outcomes, the ultimate goal/target is mucosal healing, defined by the absence of ulceration, which is associated with the best short-, medium-, and long-term outcomes for patients.

G&H What research supports the use of the treat-to-target approach in IBD?

CS The 2 most important studies have focused on Crohn's disease and include the CALM study and the REACT study. The CALM study, a multicenter, randomized, open-label, active-controlled, 48-week, phase 3 trial that was led by Dr Jean-Frederic Colombel, assessed tight control vs conventional management algorithms in adult patients with moderate to severe Crohn's disease. Assessment involved a combination of clinical plus biochemical parameters, rather than clinical parameters alone. The investigators checked these parameters at predefined intervals. If the expected improvements were not seen in these outcome measures, the therapy was either optimized or changed. Patients who achieved endoscopic remission at 48 weeks had a significantly lower risk of disease progression. The REACT trial, which was led by Dr Reena Khanna, was a cluster randomized controlled trial looking at early combined immunomodulation vs conventional management for the treatment of Crohn's disease. Again, 12 weekly reassessments occurred in the early combined immunomodulation group, which triggered therapeutic changes if remission was not achieved. Although the REACT study did not demonstrate significant improvements in symptomatic remission, patients in the early combined immunomodulation arm had a reduction in major adverse outcomes, serious disease-related complications, and the need for surgery. The REACT-2 trial is currently underway and will include mucosal healing as its endpoint.

In ulcerative colitis, there is mounting evidence that patients who achieve endoscopic and even histologic remission have a significantly lower risk of clinical relapse than patients who achieve clinical remission alone.

Thus, studies have already demonstrated, and will likely continue to demonstrate, that better long-term outcomes can be achieved with a strict treat-to-target strategy in IBD.

G&H Has this approach also been shown to impact economic outcomes?

CS Although current IBD therapies, especially biologics, are expensive, they can change the natural history of disease by achieving endoscopic healing and thus preventing long-term adverse outcomes. This is important for avoiding hospitalization and surgery, which are costly interventions. In addition, by improving the quality of life of patients, there will be a resultant reduction in absenteeism (because patients are feeling better and can work) and presenteeism (in which patients go to their job but are unable to work to their full potential). Ultimately, mucosal healing is cost-effective even though biologics are expensive.

G&H Is the treat-to-target approach applicable to all subgroups of patients with IBD?

CS Yes, there is a role for treat-to-target management across all subgroups of patients, regardless of IBD phenotype or disease duration. Tight disease control is needed to prevent adverse outcomes in all patients. Outcome assessment may vary according to disease phenotype; for example, if patients have perianal disease, the physician will look at radiologic outcomes carefully in addition to clinical and biochemical outcomes. Early treatment, or making sure that a patient is treated for subclinical inflammation before becoming overtly unwell, is very important in any patient. Most IBD practitioners are now adopting the STRIDE-II guidelines and the treat-to-target approach in clinical practice because this strategy can change clinical outcomes, including long-term ones, for patients with IBD.

G&H Are there any disadvantages or challenges to using this therapeutic approach?

CS Patient buy-in can be difficult. Some patients complain that they are reminded of their disease because they have to submit to laboratory investigations even if they are feeling well. However, ultimately, even though such testing involves time and effort from patients, the goal is for long-term disease stability and the avoidance of disease flare, surgery, and hospitalization. Symptoms should not be the only consideration when managing patients with IBD. Even if patients are feeling well, they should still undergo regular disease assessment, including CRP and fecal calprotectin testing every 3 to 6 months, as well as timely sonographic, radiologic, and endoscopic evaluations. It is much easier to treat patients when their disease is mild than once they are overtly unwell. Patients need to understand the importance of these treatment targets.

G&H Is there any evidence for instead treating patients according to drug levels?

CS A number of studies have examined proactive therapeutic drug monitoring, or the notion of treat-to-trough

(to be differentiated from treat-to-target), but this strategy has not demonstrated an improvement in clinical outcomes. An excellent meta-analysis by Nguyen and colleagues demonstrated that across 9 randomized controlled trials, proactive therapeutic drug monitoring did not produce a significant improvement in clinical remission at 1 year, nor was there a reduction in antidrug antibody formation. What it did do is cause patients to dose-escalate more frequently without necessarily improving overall outcomes. A meta-analysis by Sethi and colleagues recently looked at 26 studies, the majority of which were uncontrolled studies, and concluded that proactive therapeutic drug monitoring may be associated with some benefit in reducing treatment failure compared with standard of care and a reactive therapeutic drug monitoring approach. However, it should be noted that the meta-analysis included real-world studies, which may be subject to bias. The authors therefore concluded that larger randomized controlled trials and standardized assays are needed to substantiate their findings.

It is important not to confuse treat-to-trough with treat-to-target approaches. Drug levels are merely an adjunct to decision-making; they are not the target themselves. The ultimate goal is mucosal healing. Because of intra- and interindividual variability in drug levels, a one-size-fits-all treatment approach does not work; a threshold drug level does not necessarily correlate with mucosal healing. A treat-to-target approach with mucosal healing is still needed. Thus far, randomized controlled trials of a proactive treat-to-trough strategy utilizing anti–tumor necrosis factor (TNF) agents have not demonstrated superiority over reactive therapeutic drug monitoring whereby drug levels are checked when other parameters of disease activity are identified. Therapy is optimized accordingly if there are low drug levels in the presence of active inflammation, as this usually reflects a secondary loss of response to therapy because of the development of immunogenicity. In that scenario, therapeutic drug monitoring may help physicians optimize treatment. These exposure-response relationships are not as clear for other classes of biologics, and therapeutic drug monitoring does not have as much a role for non–anti-TNF biologics.

G&H Are there any benefits to using a treat-to-trough strategy?

CS I do not think so. This strategy typically ends up using more drug without changing overall outcomes. It is, however, important for practitioners to differentiate proactive vs reactive therapeutic drug monitoring. Are practitioners checking drug levels when a patient is completely well (ie, in clinical, biochemical, and mucosal remission) and simply reacting to a number (ie, the drug level), or are they checking drug levels because they suspect that the patient is already losing response (ie, the patient might still be feeling well but has elevated fecal calprotectin, or disease activity has been seen)? The latter case is a reactive therapeutic drug monitoring approach, not a proactive approach. As discussed, reactive therapeutic drug monitoring can be used in patients who are on anti-TNF agents as an adjunct to optimize therapy but not as an endpoint in itself.

G&H What are the priorities of research in IBD management?

CS In my opinion, the main priority for research is precision medicine and being able to determine the right drug for the right person at the right time with a goal of long-term mucosal healing. It is not possible to do this yet. Rather than having a patient start on a drug and then progress through a series of drugs, knowing biomarkers, clinical phenotypes, or other factors that could direct physicians to the best therapy could potentially prevent recurrent changes in treatment and avoid long-term complications such as hospitalization and surgery.

Disclosures

Dr Seow has served on advisory boards for Janssen, AbbVie, Takeda, Pfizer, Fresenius Kabi, Bristol Myers Squibb, Pharmascience, and Lilly. She has served as a speaker for Janssen, AbbVie, Takeda, Pfizer, and Fresenius Kabi.

Suggested Reading

Colombel JF, D'Haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and strategies to support a treat-to-target approach in inflammatory bowel disease: a systematic review. *J Crohns Colitis*. 2020;14(2):254-266.

Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet*. 2017;390(10114):2779-2789.

Khanna R, Bressler B, Levesque BG, et al; REACT Study Investigators. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet*. 2015;386(10006):1825-1834.

Nguyen NH, Solitano V, Vuyyuru SK, et al. Proactive therapeutic drug monitoring versus conventional management for inflammatory bowel diseases: a systematic review and meta-analysis. *Gastroenterology*. 2022;163(4):937-949.e2.

Sethi S, Dias S, Kumar A, Blackwell J, Brookes MJ, Segal JP. Meta-analysis: the efficacy of therapeutic drug monitoring of anti-TNF-therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2023;57(12):1362-1374.

Turner D, Ricciuto A, Lewis A, et al; 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(5):1570-1583.

Yoon H, Jangi S, Dulai PS, et al. Incremental benefit of achieving endoscopic and histologic remission in patients with ulcerative colitis: a systematic review and meta-analysis. *Gastroenterology*. 2020;159(4):1262-1275.e7.