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Management Strategies to Improve Outcomes of Patients With Inflammatory Bowel Diseases



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Strategies for management of inflammatory bowel diseases are shifting from simple control of symptoms toward full control of these diseases (clinical and endoscopic remission), with the final aim of blocking their progression and preventing bowel damage and disability. New goals have been proposed for treatment, such as treat to target and tight control based on therapeutic monitoring and early intervention. For patients who achieve clinical remission, there is often interest in discontinuation of therapy due to safety or economic concerns. We review the evidence supporting these emerging paradigms, the reasons that early effective treatment can alter progression of inflammatory bowel diseases, the importance of examining objective signs of inflammation, and the safety of reducing treatment dosage. We also discuss recent findings regarding personalization of care, including factors that predict patient outcomes and response to therapies, as well as preventative strategies.

Keywords: Intestine; Efficacy; Dose; Control.

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract characterized by periods of relapses and remission. The incidence of IBD is increasing worldwide, increasing the burden on the health care system.[1,2] The recent acknowledgment that CD is a progressive disease has changed the focus of therapeutic strategies from mere control of symptoms and improved quality of life toward blocking disease progression to prevent bowel damage and disability, which are measured by the Lemann Index in CD and the IBD Disability Index[3,4] (Figure 1*A*). Based on research of other immune-mediated diseases, such as rheumatoid arthritis (RA), new concepts have emerged and have been endorsed by international societies; these include treat to target, tight control, and disease monitoring.[5,6] All therapies for IBD target well-established disease, and even the most potent agents are not able to prevent or reverse chronic damage. Treatment during a specific window of opportunity, before bowel damage occurs, is likely to produce better outcomes.

However, uninterrupted lifelong therapy with potent immunosuppressive agents is probably unsustainable, so de-escalation strategies should be explored. One of the most important issues in IBD care is dealing with patients' heterogeneity, and success depends on our ability to personalize care by identifying factors that better predict outcomes and responses to therapy. There is increasing evidence that in IBD, like in other immune-mediated diseases, a period of immunologic change precedes symptoms and perhaps even organ injury and occurs years before diagnosis.[7–10] Gaining a better understanding of this window could lead to strategies to prevent IBD.

Treat to Target

The concept of treat to target has been studied for several years in chronic diseases, such as diabetes and hypertension.[11,12] For patients with RA, the treat to target recommendations, formulated in 2010 and since updated, have confirmed clinical remission as a target, defined as the absence of signs and symptoms of significant inflammatory disease activity.[5] For patients with IBD, this concept arose from the observation that therapeutic strategies failed to alter progression of IBD[13] and from the frequent discordance between symptoms and objective measures of disease activity. In a post-hoc analysis of the data from the SONIC (Study of Biologic and Immunomodulator Naive Patients in

Abbreviations used in this paper: CD, Crohn's disease; CRP, C-reactive protein; FCP, fecal calprotectin; IBD, inflammatory bowel diseases; RA, rheumatoid arthritis; TNF, tumor necrosis factor; UC, ulcerative colitis.

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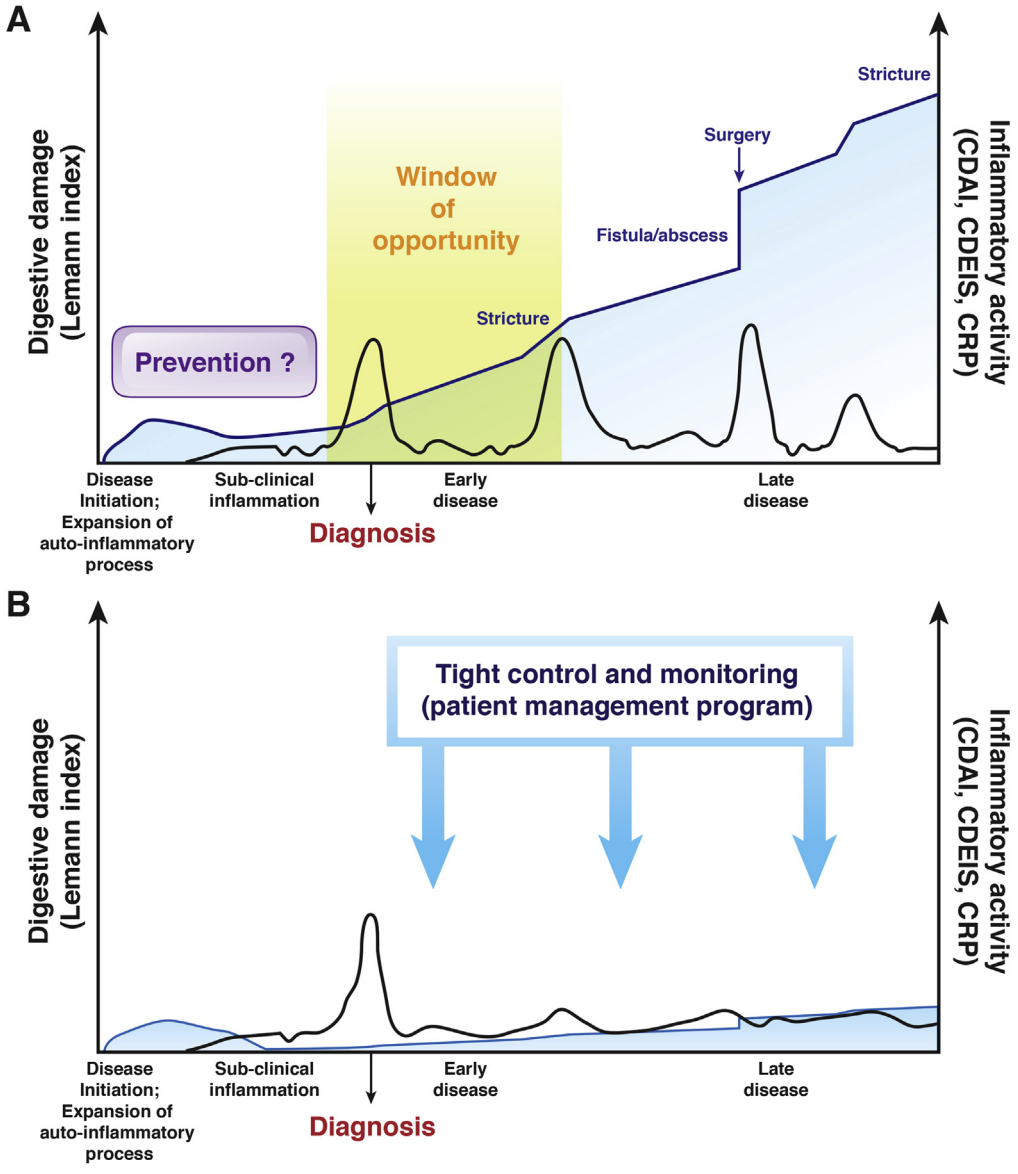

Figure 1. Detection and treatment of IBD before symptoms. (*A*) Progression of cumulative digestive damage (measured by the Lemann Index) and inflammatory activity (measured by symptoms, endoscopy, and biomarkers) in patients with CD. Early effective treatment during the window of opportunity with disease-modifying agents could block disease progression and damage. There is evidence that years before diagnosis and development of symptoms, alterations to the immune response occur (marked by increases in circulating levels of antimicrobial markers and levels of cytokines) that the stage for IBD. A better understanding of the earliest phase of disease (preclinical disease) could offer a chance for developing successful interventions for future prevention. (*B*) Early effective treatment during this window of opportunity could slow disease progression and prevent damage.

Crohn's Disease) trial, half of the patients receiving azathioprine or infliximab, or both, who were in remission had evidence of residual active CD, based on endoscopy or C-reactive protein (CRP) measurement, whereas other patients with endoscopic and CRP normalization had persistent clinical symptoms.[14] In patients with UC, symptoms usually correlate with endoscopic activity—only 20% of patients in clinical remission still have significant endoscopic disease activity,[15] but complete normalization of stool frequency is not always observed in patients with endoscopic healing.[16]

Switching the target from clinical remission to endoscopic healing has mainly been supported by post-hoc analysis of clinical trials. In the step-up/top-down study of patients with CD, complete endoscopic healing (defined as a simple endoscopic score of 0) after 2 years of therapy was the only factor that predicted sustained, steroid-free remission at 3 and 4 years after therapy was initiated.[17] Deep remission has been empirically defined as clinical and endoscopic remission.[18] In an exploratory study of patients with moderate to severe ileocolonic CD who received adalimumab induction and maintenance therapy (the EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing [EXTEND] study), those in deep remission at 1 year had fewer hospitalizations and CD-related surgeries than those not achieving deep remission.[18] In ACT (Active Ulcerative Colitis Trials)-1 and ACT-2, endoscopic healing after 8 weeks of infliximab correlated with lower rates of colectomy at 1 year.[19]

The STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) program was initiated by the International Organization for the Study of Inflammatory Bowel Diseases[20] (Figure 2). It examined potential treatment targets for IBD to be used for a treat-to-target clinical management strategy using an evidence-based expert consensus process. The selected target for UC was clinical/patient-reported