ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Early Intervention in Crohn's Disease

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G&H What biologic features of Crohn's disease support the rationale for early intervention?

BS Crohn's disease is a chronic, progressive, transmural inflammatory disease in which ongoing inflammation can lead to irreversible bowel damage over time, including fibrosis, stricture, fistula, abscess, and the need for surgery. Although inflammatory lesions are often highly responsive to therapy early in the disease course, chronic structural complications become difficult to reverse once established. This progressive nature of Crohn's disease has led to the concept of a therapeutic window of opportunity during which effective control of inflammation may prevent progression from inflammatory disease to a stricturing or penetrating phenotype. Studies have shown that early introduction of biologic or immunosuppressive therapy is associated with delayed phenotype progression and improved long-term outcomes. One of the strongest biologic arguments for early intervention is fibrosis. Chronic intestinal inflammation promotes tissue remodeling and fibrotic stricture formation, yet these complications respond poorly to currently available medical therapies, and no approved antifibrotic therapy currently exists for Crohn's disease. Consistent with this concept, bowel damage accumulates progressively over time, with median Lémann Index scores increasing nearly 20-fold, from 0.9 within the first 2 years after diagnosis to 16.5 after more than 10 years of disease, highlighting the cumulative and potentially irreversible nature of longstanding inflammation. Finally, early biologic therapy has been associated with higher rates of transmural healing, which in turn have been linked to lower risks of bowel damage progression, surgery, and treatment escalation. Together, these findings support a proactive strategy focused not only on symptom control, but also on prevention of long-term structural damage and disability.

G&H How can clinicians identify patients with Crohn's disease who are most likely to benefit from early advanced therapy?

BS Identifying patients most likely to benefit from early advanced therapy requires moving beyond the consideration of symptoms alone. Because clinical symptoms often correlate poorly with the true inflammatory burden in Crohn's disease, some patients with relatively mild symptoms may already have extensive transmural inflammation or early bowel damage at diagnosis. Several clinical features have consistently been associated with a more aggressive disease course and a higher risk of complications. These include young age at diagnosis, extensive bowel disease, deep ulcerations, perianal disease, penetrating and stricturing phenotypes, elevated inflammatory biomarkers, and early corticosteroid requirements. Objective assessment is therefore essential. Endoscopy helps define disease extent and severity, whereas cross-sectional imaging and intestinal ultrasound can identify transmural inflammation, fistula, abscess, and early structural complications that may not yet be clinically apparent. Importantly, studies suggest that the treatment of higher-risk patients early in the disease course is associated with significantly lower rates of hospitalization and bowel resection. As a result, modern management increasingly emphasizes early risk stratification and proactive disease control before irreversible bowel damage develops.

G&H How has the PROFILE study influenced current thinking about early intervention in Crohn's disease?

BS The PROFILE study has provided some of the strongest prospective evidence supporting early intervention in patients with newly diagnosed Crohn's disease. In this multicenter randomized trial, patients treated with early combined infliximab and immunomodulator therapy achieved substantially better outcomes than those managed with an accelerated step-up approach. Patients receiving early intensive therapy had markedly higher rates of sustained corticosteroid-free and surgery-free remission, along with lower rates of hospitalization, disease flare, and abdominal surgery. The study also demonstrated superior endoscopic outcomes in the top-down group. Importantly, the PROFILE study reinforced the concept that there may be a narrow therapeutic window early in the disease course during which inflammation is more amenable to disease modification.

More recently, 5-year follow-up data presented at Digestive Disease Week 2026 provided some of the strongest long-term evidence supporting this concept. Patients treated with infliximab-based combination therapy from diagnosis had an approximately 5-fold lower risk of abdominal surgery, lower rates of progression to stricturing or penetrating disease, and fewer Crohn's disease–related hospitalizations compared with those managed using a step-up strategy.

Although biomarker-based risk stratification did not demonstrate the expected clinical utility, the PROFILE study has significantly influenced current thinking by showing that treatment timing matters. The trial suggested that delaying effective therapy may allow ongoing inflammation to persist and disease progression to continue, potentially leading to cumulative bowel damage and irreversible structural complications. Taken together, these findings support the broader principle that early effective therapy may improve long-term outcomes and alter the trajectory of disease progression in selected patients with newly diagnosed Crohn's disease.

G&H Overall, what are the major clinical benefits associated with this approach?

BS Early intervention in Crohn's disease has been associated with improved rates of corticosteroid-free remission, mucosal healing, and potentially transmural healing. Several studies have also demonstrated reductions in hospitalization, corticosteroid exposure, disease flare, and surgery among patients treated earlier in their disease course. One of the major goals of early intervention is the prevention of cumulative bowel damage by controlling inflammation before irreversible structural complications develop. Early advanced therapy may reduce progression to stricturing or penetrating phenotypes, thereby decreasing the long-term risk of bowel resection and disability. Importantly, early biologic therapy has also been associated with a higher rate of transmural healing, which appears to predict improved long-term outcomes and a low rate of bowel damage progression. These observations have contributed to a broader shift from symptom-based management toward a treat-to-target strategy focused on objective measures of inflammation. This approach is reflected in the STRIDE-II guidelines, which emphasize objective disease control using biomarkers and endoscopic healing, rather than symptom assessment alone. These findings suggest that the benefits of early intervention extend beyond short-term symptom improvement and may ultimately translate into better long-term disease control and quality of life.

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G&H Has research demonstrated that early intervention is cost-effective?

BS Increasing evidence suggests that early intervention with anti–tumor necrosis factor (TNF) therapy in Crohn's disease is cost-effective and, in some analyses, economically advantageous compared with conventional step-up care. Several economic models have demonstrated that initiating anti-TNF therapy early in the disease course may improve long-term clinical outcomes while reducing overall health care expenditure. Although biologic therapy carries higher upfront cost, this expense may be offset by reductions in hospitalizations, surgery, corticosteroid exposure, disease flare, and other disease-related complications. A Canadian Markov model demonstrated that initiating anti-TNF therapy within the first 2 years

after diagnosis resulted in better long-term outcomes and substantially lower overall cost compared with later initiation. Pediatric data have also shown that early infliximab biosimilar therapy may achieve superior clinical outcomes without increasing total health care costs, as higher drug expenditure is balanced by lower downstream disease management costs. Importantly, the increasing availability of biosimilars has further improved the economic feasibility of early biologic use. However, most cost-effectiveness data currently involve anti-TNF agents, particularly infliximab and adalimumab, and whether similar economic benefits apply to other advanced therapies remains uncertain.

G&H Could you discuss the evidence that early intervention truly modifies the natural history of Crohn's disease?

BS Accumulating evidence suggests that early intervention can modify the natural history of Crohn's disease. The concept of disease modification has evolved from a theoretical goal to an increasingly measurable clinical outcome. Evidence supporting this concept has steadily grown over the past 2 decades. In the REACT trial, early combined immunosuppression was associated with a 27% reduction in major adverse outcomes and a 31% reduction in surgery compared with conventional management, providing some of the first prospective evidence that earlier effective therapy may improve long-term outcomes.

More recently, transmural healing has emerged as a potential marker of disease modification. In a recent multicenter prospective study, initiation of biologic therapy within 12 months of diagnosis was associated with a more than 3-fold higher likelihood of achieving transmural healing (adjusted odds ratio, 3.23). Importantly, transmural healing was independently associated with lower risks of bowel damage progression, surgery, and treatment escalation, outcomes that are closely linked to long-term disease progression and disability.

All of these findings provide compelling evidence that early intervention can alter the long-term trajectory of Crohn's disease and support the existence of a therapeutic window of opportunity before irreversible bowel damage becomes established.

G&H Are there any potential risks or limitations to this approach?

BS Although early intervention offers important potential benefits, this strategy must be balanced against the risks of overtreatment, long-term immune suppression, and increased health care costs. Safety considerations vary according to patient characteristics and therapeutic mechanisms. Anti-TNF agents may increase the risk of serious infection, and immunomodulators have historically raised concerns regarding lymphoma and nonmelanoma skin cancer in select populations. Older patients and individuals with significant comorbidities may require more individualized therapeutic decisions and a careful risk-benefit assessment. Another important limitation is that not all patients with Crohn's disease experience a progressive disease course. Some individuals may follow a relatively indolent trajectory and therefore may not require aggressive upfront therapy. As a result, improved risk stratification remains critical to avoid unnecessary exposure to advanced therapy in low-risk patients. In addition, most prospective data supporting early intervention involve an anti-TNF–based strategy, particularly combination therapy with immunomodulators. As newer advanced therapies become increasingly available, we are still learning about the true magnitude of their benefit in early Crohn's disease and how these outcomes compare with those historically observed with anti-TNF–based early intervention strategies. Finally, despite the growing evidence supporting a therapeutic window of opportunity, the optimal time, duration, and sequencing of early intervention therapies have not yet been fully defined.

G&H How has the definition of early Crohn's disease evolved over time?

BS Historically, early Crohn's disease was defined primarily according to disease duration, within the first 18 to 24 months after diagnosis. This definition was largely based on the assumption that inflammatory disease predominates early in the disease course before structural complications become established. Over time, however, it has become increasingly clear that disease duration alone does not adequately capture the biologic stage of Crohn's disease. Some patients already present with stricture, fistula, or significant bowel damage near diagnosis, whereas others may follow a more indolent course for many years. As a result, the concept of early Crohn's disease has progressively evolved beyond a purely time-based definition. Increasingly, early disease is viewed through a biologic lens, reflecting the stage at which inflammatory processes remain potentially modifiable before the development of cumulative bowel damage. However, the precise criteria that should define this stage remain incompletely established and continue to evolve. Consequently, early intervention is increasingly viewed as treatment initiated before fibrosis, irreversible bowel damage, and transmural complications develop. This evolving concept has also emphasized the importance of timely diagnosis, objective assessment of inflammatory burden, and early

stratification using biomarkers, endoscopy, and cross-sectional imaging. Ultimately, the concept of early intervention is becoming less about time from diagnosis alone and more about intervening during a therapeutic window in which disease progression may still be modifiable.

G&H What are the major unanswered questions and future research priorities in early intervention?

BS Although the field has advanced substantially, several important questions remain unanswered regarding early intervention in Crohn's disease. One of the greatest priorities is improving risk stratification. Better clinical, molecular, genetic, microbiome, and imaging biomarkers are needed to identify which patients are most likely to develop progressive disease and therefore can reap the greatest benefit from early advanced therapy. Avoiding overtreatment in lower-risk patients remains equally important. Another key area of research involves defining the optimal therapeutic target. Although mucosal healing has become a central goal, increasing attention is now being directed toward deeper endpoints such as transmural healing, prevention of bowel damage progression, and long-term disability reduction. Additional studies are needed to determine whether newer advanced therapies can achieve the same degree of disease modification historically observed with an anti-TNF–based strategy. Questions regarding the optimal sequencing, combination, and duration of therapy also remain incompletely answered. Another emerging area of interest is the preclinical phase of Crohn's disease. Increasing evidence suggests that immunologic, microbial, and inflammatory abnormalities may precede clinical diagnosis by several years. Understanding this preclinical stage could eventually allow earlier identification of high-risk individuals and open the possibility of a preventive or disease-intercepting strategy before bowel damage develops. Future research will likely increasingly focus on a precision medicine approach, including biomarker-guided therapy selection, individualized treatment algorithms, and integration of artificial intelligence and advanced imaging techniques into clinical decision-making. Ultimately, the major challenge moving forward will be learning how to deliver the right therapy to the right patient at the right time while maximizing long-term disease control and minimizing unnecessary treatment exposure.

Disclosures

Dr Silva has served as a speaker for AbbVie, Johnson & Johnson, and Takeda, and has received scientific/educational support from these companies.

Suggested Reading

Banerjee R, Pal P, Girish BG, Reddy DN. Risk factors for diagnostic delay in Crohn's disease and their impact on long-term complications: how do they differ in a tuberculosis endemic region? *Aliment Pharmacol Ther*. 2018;47(10):1367-1374.

Beilman CL, Kirwin E, Ma C, McCabe C, Fedorak RN, Halloran B. Early initiation of tumor necrosis factor antagonist-based therapy for patients with Crohn's disease reduces costs compared with late initiation. *Clin Gastroenterol Hepatol*. 2019;17(8):1515-1524.e4.

Chang YC, Lin SH, Chen TD, et al. Very early biologic therapy within six months of Crohn's disease diagnosis improves one-year steroid-free clinical remission: a retrospective cohort study [published online January 9, 2026]. *Digestion*. doi:10.1159/000550394.

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.

Noor NM, Davies N, Tahir W, et al; PROFILE Study Group. Anti-tumor necrosis factor treatment from diagnosis is more effective and less costly than conventional "step-up" care for patients with active Crohn's disease: a cost-effectiveness analysis from the PROFILE trial. *J Crohns Colitis*. 2025;19(9):jjaf150.

Noor NM, Lee JC, Bond S, et al; PROFILE Study Group. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2024;9(5):415-427.

Revés J, Fernandez-Clotet A, Ordás I, et al. Early biological therapy within 12 months of diagnosis leads to higher transmural healing rates in Crohn's disease. *Clin Gastroenterol Hepatol*. 2025;23(7):1194-1203.e2.

Revés J, Mascarenhas A, José Temido M, et al. Early intervention with biologic therapy in Crohn's disease: how early is early? *J Crohns Colitis*. 2023;17(11):1752-1760.

Vuijk SA, Jongsma MME, Hoeven BM, et al. Randomised clinical trial: first-line infliximab biosimilar is cost-effective compared to conventional treatment in paediatric Crohn's disease. *Aliment Pharmacol Ther*. 2024;59(12):1510-1520.