The Role of Early Biologic Therapy in Inflammatory Bowel Disease

Dana Rachel Berg, MD, * *Jean-Frederic Colombel, MD,*[†] *and Ryan Ungaro, MD, MS*[†]

The goals for treatment of inflammatory bowel diseases (IBDs) are changing from elimination of symptoms toward complete disease control—a process that demands both clinical and endoscopic remission. This new IBD treatment paradigm has been shifting from a conventional "step-up" approach toward a more "top-down" early intervention treatment strategy. Recent studies suggest that the use of biologic agents, specifically those targeting tumor necrosis factor alpha, earlier in the treatment course improves patient outcomes and can prevent progression to irreversible bowel damage. Although the strategy of early intervention has accumulating evidence in Crohn's disease, there is less evidence supporting its impact in ulcerative colitis.

Key Words: inflammatory bowel disease, crohn's disease, ulcerative colitis, early biologic therapy, top-down therapy.

INTRODUCTION

Inflammatory bowel diseases (IBDs), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract characterized by a relapsing and remitting course.[1, 2] With many potential etiologic factors, IBD is thought to result from an aberrant mucosal immune response to environmental factors in a genetically susceptible individual.[3–5] Recent acknowledgement that IBD—particularly CD—is a progressive disease has changed the focus from mere control of symptoms toward impeding the development of irreversible bowel injury. At present, all therapeutic interventions in IBD target inflammatory disease and are unable to reverse chronic bowel wall damage once it has emerged.

The stricturing and penetrating complications that can develop in CD are likely manifestations of uncontrolled inflammation. When examining a cohort of 306 CD patients from the United States, Thia et al. showed that the cumulative risk of developing either stricturing or penetrating disease was 33.7% at 5 years and 50.8% at 20 years after CD diagnosis.[6] Cosnes et al. demonstrated that the 20-year rates of inflammatory, structuring, and penetrating disease were 12%, 18%, and 70%, respectively.[7] Additionally, in a given year, about 3%–5% of CD patients will require CD-related surgery.[8] To

halt this natural progression of disease and prevent the need for surgery, therapeutic treatment should be implemented before the occurrence of permanent bowel damage and resulting disability.

Conventional "step-up" therapy requires failure of corticosteroids, mesalamine, and thiopurines before considering biologic therapy. However, as the data regarding biologic therapy evolve, there is increasing evidence that early initiation of biologics in moderate to severe disease—before failure of conventional therapy—allows for optimal patient outcomes. There is likely a "window of opportunity" where early effective therapy can significantly alter disease progression via a "top-down" approach.

Substantial evidence supports earlier use of biologics such as anti–tumor necrosis factors (anti-TNFs; eg, infliximab, adalimumab, and certolizumab) in CD. For example, post hoc analyses of clinical trials and prospective studies on early biologic CD intervention have reported superior clinical outcomes in patients with shorter disease duration. In post hoc analysis of the CHARM and ADHERE trials, Schreiber et al. reported a 15% improvement in remission rates for patients starting adalimumab within the first 2 years of diagnosis compared with after 5 years of disease (43% vs 28%; *P* < 0.001).[9] It is unclear, however, whether the advantages associated with early anti-TNF use in CD apply to the new anti-integrin (vedolizumab) and anti-IL12/23 (ustekinumab) therapeutic biologic agents.

It is similarly unclear whether the above-mentioned "top-down" paradigm is equally valid in UC. The data regarding utility of early biologic therapy in UC patients remain sparse. There is, however, evidence that UC is also a progressive disease and can ultimately result in strictures,[10, 11] pseudopolyposis,[12–14] bridging fibrosis,[15] dysmotility,[16, 17] and anorectal incontinence.[18–20] Additionally, 10 years after diagnosis, approximately 10% of UC patients will require a colectomy for management of disease-related complications.[21] Although surgery remains

an important component of UC management and can allow patients to regain quality of life, it is not without risks, as nearly 30% of patients will have a postoperative complication.[22] The aim for early therapy in UC would therefore be to halt disease progression and prevent, or at least delay, the need for a total colectomy with ultimate ileal pouch anal anastomosis (IPAA).

Herein, we conducted an extensive review of the literature and describe the current evidence on early biologic intervention in patients with IBD.

METHODS

A literature search was carried out for relevant articles written between 1964 and 2017. Most of the information was retrieved from articles published between 2008 and 2018. We searched the PubMed libraries using the following individual and combined key words: Crohn's disease, ulcerative colitis, inflammatory bowel disease, early intervention, early disease, progressive disease, biologic agents, anti-TNF agents, anti-metabolites, immunomodulators, infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab, biosimilars, biologic cost, and risk prediction models. References cited in the articles were also searched to identify other potential sources of information.

Defining Early Disease

To create a universal language for defining early CD, an international group of IBD experts developed the "Paris Definition," which takes into account disease duration and previous use of disease-modifying agents.[23] According to this consensus, early CD is defined as ≤18 months (determined by time since diagnosis, not symptom onset) and no prior or current treatment with disease-modifying drugs (eg, immunomodulators or biologics). In contrast, there is currently no guidance on how to define early disease in UC.[23] It is important to note that these definitions are based on expert opinion; there are no specific studies looking at how to best define early IBD.

Early Disease as a Distinct Entity

There is a basic science underpinning for defining early IBD as a distinct entity. In both experimental murine models and humans, there are distinct changes in cytokines and expression of adhesion molecules during the early course of the disease. To delineate the immunologic differences between early and late IBD, a longitudinal study was conducted to assess the changes in mucosal immune response in IL-10-deficient mice.[24] The results of this study revealed that the development of colitis in these mice is characterized by 2 distinct cytokine phases. IL-12 plays an influential role in early colitis, whereas late disease (>25 weeks) is defined by the loss of IL-12 and the synthesis of IL-4 and IL-13. These findings suggest that the underlying immune mechanisms of early and late colitis are, in fact, different. Further substantiating this claim, neutralizing antibody to IL-12 reversed early, but not late, disease in this study.[24, 25]

Kugathasan et al. further investigated the effect of IL-12 in pediatric IBD patients, and the results, which complement those of animal studies, highlight the pathogenic role of IL-12 and its importance in early CD. Significantly higher levels of IL12p40 and IL12Rβ2 messenger RNA were found in children with early compared with late CD. There was similarly a striking elevation of INF-γ production by T cells in response to IL-12 by T cells in early, but not late, CD. One can therefore speculate that antibody blockade of IL-12 or related pathways during the initial manifestations of pediatric IBD, rather than once it has progressed to chronic later stages, will result in improved therapeutic outcomes.[26]

Zorzi and colleagues performed a similar study in the adult population using postoperative disease as an early Crohn's disease model.[27] The aim was to assess the pattern of cytokine expression at different stages of disease progression. To this end, "early lesions" were those developing in the neo-terminal ileum after a curative ileo-colonic resection, and "established lesions" were those developing in the terminal ileum due to long-standing disease requiring resection. When examining mucosal biopsies from these patients, they found that the "early lesions" contained high levels of interferon (IFN)-γ and interleukin (IL)-21. IL-12, a strong inducer of IFN-γ and IL-21 production, was also elevated in the neo-terminal ileum biopsies. These same biopsies were similarly associated with a slight increase in IL-17A and elevated levels of TNF-α. In biopsies taken from areas with "established lesions," there was marked upregulation of IL-17A and induction of IL-23 and IL-6. Samples from established lesions also revealed elevated levels of IFN-γ, IL-17A, IL-4, and IL-5 as compared with normal controls.[27]

Both Zorzi et al. and Kugathasan et al. revealed that IL-12 and IFN-γ are overproduced in the gut of patients with early-stage disease compared with that of late disease. These findings substantiate that the most effective therapeutic modalities may differ when directed at particular cytokines during early vs late disease development.

EARLY INTERVENTION WITH ANTI-TNF AGENTS IN CD

The development of biologic agents that target and neutralize TNFα was a revolutionary advancement in CD treatment, leading to improved clinical outcomes including mucosal healing.[28–30] Conventional CD management has involved a "step-up" approach featuring sequential use of corticosteroids, immunomodulators, and then anti-TNF agents. However, recent guidelines have changed to emphasize earlier use of anti-TNF biologic agents in moderate to severe CD.[31]

Infliximab

TOP-DOWN trial

One of the first studies to suggest a benefit of early biologic therapy was the TOP-DOWN trial.[32] This was a 2-year

open label randomized trial at 18 centers in Belgium, Holland, and Germany. The study aimed to compare the efficacy of early combined immunosuppression (infliximab and azathioprine) with conventional management (eg, corticosteroids, followed sequentially by azathioprine and infliximab as needed) in patients with recently diagnosed CD. On average, CD was diagnosed in study participants less than 4 months before randomization. The primary outcome was corticosteroid-free remission without bowel resection at weeks 26 and 52. At week 26, 60% of patients in the early combined immunosuppression group were in remission without corticosteroids and without surgical resection, compared with 35.9% of those receiving conventional management ($P = 0.0062$). Remission rates at week 52 were 61.5% and 42.2% in the early vs conventional group, respectively ($P = 0.278$). In addition, patients assigned to combined immunosuppression showed a more rapid drop in their Crohn's Disease Activity Index (CDAI) scores than the conventional group and had a more rapid reduction in the median serum concentration of C-reactive protein (CRP) by week 10. In long-term follow-up (week 104), no ulcers were seen on colonoscopy in 73.2% of patients assigned to the early combined immunosuppression group compared with 30.4% of controls ($P = 0.0028$).

These findings suggest that in patients with early CD, use of early combined immunosuppression results in remission more quickly and at higher rates than conventional "step-up" management. One caveat of this study is that patients in the combined immunosuppression group received episodic treatment with infliximab rather than scheduled doses. At the time of this study, scheduled infliximab maintenance dosing was not yet standard practice, which may account for the smaller difference in patient outcomes at 52 weeks.

SONIC trial

In a post hoc analysis of the seminal Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial,[33] different composite remission measures were evaluated at week 26, including clinical remission (CR), mucosal healing (MH), and biological remission (C-reactive protein normalization [CRP_{norm}]). These composite remission parameters were stratified by disease duration with a focus on patients with early CD, defined as disease duration ≤18 months, no previous use of immunosuppressants or biologics, and no fistulas. Among this subgroup of early CD, a higher proportion of patients achieved different composite remission measures with combination therapy (ranging from 63% to 76.5%) compared with either infliximab (25% to 50%) or azathioprine monotherapy (10% to 30%). More than 80% of early CD patients receiving combination therapy achieved CR, more than 60% achieved the composite end point of CR + MH, and 65% achieved CR + MH + CRP_{norm}. The SONIC data therefore demonstrate improved results for patients treated with combination therapy within 18 months of diagnosis.

Adalimumab

CHARM, ADHERE, and EXTEND trials

Data from clinical trials on adalimumab also suggest increased benefit in patients with shorter disease duration. The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM)[34] was a large phase III randomized, double-blind, placebo-controlled study demonstrating the efficacy of adalimumab in moderate to severe CD. In a post hoc analysis[9] of all randomized patients in this trial, the impact of disease duration on clinical outcomes was examined. Patients from CHARM were divided into 3 disease duration subgroups: <2 years, 2 to <5 years, and ≥5 years. Clinical remission and response rates at weeks 26 and 56 were compared between those administered adalimumab vs placebo, and were also assessed through 3 years in the ADHERE[35] extension trial. Shorter disease duration was a significant predictor of higher remission rates. Specifically, patients with disease duration <2 years maintained higher remission rates than patients with longer disease duration through 3 years of treatment.

This post hoc analysis of the CHARM trial also noted increasing rates of overall adverse events, with increasing duration of CD in adalimumab-treated patients. The risk of hospitalization during the CHARM period was lowest in the shortest–disease duration subgroup and highest in the longest–disease duration patients. Additionally, patients with longer duration of CD had higher CDAI scores, were older, and were slightly more likely to have fistulas. These findings suggest that the patients with longer disease duration had greater degrees of bowel damage. These combined results elucidate the potential benefit in initiating biologic therapy early in the disease course before development of irreversible bowel injury.

In the EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing (EXTEND) study, patients with shorter disease duration were similarly more likely to achieve deep remission, defined as the absence of mucosal ulceration and CDAI scores <150. After 1 year of treatment, 33% of patients with a disease duration ≤2 years were in deep remission, compared with 20% with a disease duration of 2–5 years and 16% in those with >5 years' duration.[33, 36]

Certolizumab

PRECISE 2 trial

Data from clinical trials on certolizumab suggest increased benefit in patients with shorter disease duration. The double-blind, randomized, placebo-controlled PRECISE 2 trial demonstrated the efficacy and safety of certolizumab pegol (400 mg) in moderate to severe CD over 26 weeks.[37] In a post hoc analysis,[38] the efficacy (response and remission) data from the PRECISE 2 trial were analyzed according to disease duration. Response rates were significantly higher in patients

treated with certolizumab pegol early in the disease course than in those who started treatment later on in the disease. The response rate at 26 weeks was 89.5% in patients with disease duration <1 year (P < 0.01 vs placebo), compared with 57.3% in patients with CD for ≥5 years (P < 0.001 vs placebo). Remission rates showed a similar trend.

Observational Data With Anti-TNF Agents

To better understand outcomes in a "real-world" setting, Rubin et al. conducted an analysis of health claims data to assess the impact of a top-down approach with early introduction of anti-TNF therapy.[39] Three patient groups were identified: a group that used 5-ASA and/or corticosteroids and/or immunosuppressants (IS) before anti-TNF therapy (called "Step-Up"); an immunosuppressant (IS) to TNF inhibitor group, which used immunosuppressive therapy (not 5-ASAs) before anti-TNF (called "IS-to-TNF"); and a group that initiated anti-TNF therapy within 30 days of the first administrative code for CD (called "Early-TNF"). Response to anti-TNF therapy was measured out to 24 months after anti-TNF initiation and was defined as continued corticosteroid use, CD-related surgery, anti-TNF dose escalation, and anti-TNF discontinuation/ switch. The results demonstrated that earlier use of anti-TNF therapy is associated with a significantly higher response rate than the Step-Up or IS-to-TNF strategies, with lower rates of corticosteroid use, reductions in loss of response, and fewer surgeries.[39] This study suggests that in "real-world" health claims data, a "top-down" strategy in CD resulted in improved outcomes compared with conventional "step-up" management.

Other studies have similarly revealed the benefits of early anti-TNF therapy in CD patients. For example, in a retrospective analysis by Mandel et al.,[40] hospitalization rates decreased significantly in CD patients with early (within 3 years from diagnosis; P = 0.016) but not late anti-TNF exposure. Another large cohort study by Safranoova et al.[41] revealed that treatment with immunomodulators or anti-TNF agents within the first 2 years of CD diagnosis is associated with reduced risk of developing new bowel strictures (P = 0.004 for immunomodulators and P = 0.018 for TNF antagonists). This Swiss IBD cohort study therefore suggests that immunosuppressive therapy with immunomodulators and/or TNF antagonists can reduce structural bowel damage when introduced in the early stages of disease.

Data on the effect of early immunosuppression to time of surgical intervention remain limited. One retrospective cohort study[42] by Ma et al. investigated the impact of early (within the first 2 years of disease) CD treatment with anti-TNF agents on the rate of surgical resection. All 190 CD outpatients included in the study were primary responders to anti-TNF therapy and were followed during maintenance with either infliximab or adalimumab. Patients were stratified by disease duration at the time of anti-TNF initiation, with a median follow-up of 154.4 weeks. Patients in the late anti-TNF cohort were >5 times more likely to require surgery than early anti-TNF initiators (30.7% vs 5.7%; P < 0.001). In Kaplan-Meier analysis, early initiation of anti-TNF therapy not only prolonged time to surgery (P = 0.001) but also time to secondary loss of response (P = 0.006).

Data From Pediatric Populations

Childhood-onset IBD usually presents with more extensive symptoms and more severe disease progression than adult-onset IBD.[43–45] Similar to adults, standard therapy for children newly diagnosed with CD has conventionally been treatment with corticosteroids followed by an immunomodulator (IM). Although IM use has demonstrated efficacy in this patient population, the onset of action may be delayed for months, side effects are common including risk for malignancy, and preexisting growth abnormalities often do not resolve with IM therapy.[46, 47] Due to the aforementioned risks associated with IM use, anti-TNF therapy has become well accepted in this young patient population, with accumulating data suggesting earlier use.

To address the benefit of early anti-TNF therapy in the pediatric population, the Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (RISK) study[46] was performed. In this inception cohort of pediatric CD patients, the authors examined the impact of anti-TNF therapy within 3 months of diagnosis on 1-year outcomes compared with early IM treatment. Results revealed that early treatment with anti-TNF therapy was superior to early IM (85.3% vs 60.3% in clinical remission; P = 0.0017). Early IM therapy was no different than no early immunotherapy in achieving remission at 1 year (60.3% vs 54.4% in clinical remission; relative risk, 1.11; 95% confidence interval, 0.83–1.48; P = 0.49). Additionally, the mean height z-score increased compared with baseline in the anti-TNF group alone.

In another small pediatric study,[48] Kim et al. set out to evaluate the efficacy of "top-down" vs "step-up" treatment regimens in those with pediatric CD. Twenty-nine pediatric CD patients given infliximab at the Samsung and Chungnam National University Hospital were identified. Eleven patients refractory to conventional therapy were included in the "step-up" group for infliximab treatment. Eighteen infliximab-treated moderate to severe CD patients who had not previously been exposed to corticosteroids or IM were considered the "top-down" group. The duration from the initial diagnosis to infliximab infusion was 11.5 ± 7.4 months and 0.8 ± 0.6 months for the step-up and top-down groups, respectively. The efficacy of treatment was assessed by comparing Pediatric Crohn's Disease Activity Index (PCDAI) scores. At 8 weeks, clinical remission was achieved in 3 out of 11 patients in the step-up group and in 16 out of 18 patients in the top-down group (P = 0.001). Additionally, after 1 year, the perianal fistulas were completely closed in 100% of

those allocated to the top-down management plan, compared with 50% of the step-up patients.

A similar retrospective study was conducted evaluating the efficacy of the infliximab "top-down" and "step-up" strategies in moderate to severe pediatric CD but looking at longer-term outcomes at 3 years.[49] A total of 31 patients (group A) were treated with early infliximab induction ("top-down"), and 20 patients (group B) refractory to conventional therapy underwent infliximab treatment ("step-up"). This study found that the "top-down" strategy outperformed the "step-up," with higher relapse-free rates (35.5% vs 15%; $P = 0.0094$) and remission rates (92.1% ± 7.2% vs 78.3% ± 16.6%; $P = 0.005$) over 3 years. Additionally, multivariable analysis showed that the duration from the initial diagnosis to infliximab introduction was the only factor associated with relapse-free remission at 3 years.

There are fewer data on the impact of early anti-TNF therapy on mucosal healing (MH) in pediatric CD. However, a recent study[50] by Kang et al. examined the impact of early vs late combined immunosuppression on MH. A prospective cohort of 76 CD patients treated with infliximab and azathioprine were divided into those who had a conventional "step-up" approach and those who received combination therapy within 1 month of diagnosis. At week 54, patients who received early combination therapy had significantly higher rates of MH compared with those who stepped up to combined immunosuppression (74% vs 42%; $P = 0.007$). The effectiveness of these agents within 1 month of diagnosis also suggests that the window of opportunity may be shorter than previously anticipated in the pediatric population.

The rates of applying an early "top-down" approach in pediatric to young adult (≤24 years of age) CD were more broadly assessed in a health claims database study. Health insurance claims from 2009 to 2013 were analyzed with a "top-down" approach, defined as new anti-TNF therapy within 30 days of first IBD medication prescription. On the contrary, a conventional "step-up" approach was defined as anti-TNF therapy >30 days after first IBD medication prescription.[51] A total of 11,962 patients with incident IBD were followed for a mean of 657 days. Among the 3300 patients taking anti-TNF therapy, 1298 (39.3%) were treated with the "top-down" and 2002 (60.7%) with the "step-up" approach. The proportion of patients receiving top-down treatment increased over the study period from 31.4% in 2009 to 49.8% in 2013. Patients who received "top-down" treatment were less likely to use corticosteroids (32.5% vs 94.2%; $P < 0.0001$), 5-aminisalicylates (17.3% vs 75.1%; $P < 0.0001$), or thiopurines (13.5% vs 54.8%; $P < 0.0001$) compared with "step-up" patients. These results demonstrate that the utilization of a top-down strategy has increased over the years in younger patients, with a shorter duration of time between IBD diagnosis and initiation of anti-TNF therapy. In addition, early anti-TNF treatment is related to lower rates of corticosteroid, 5-aminisalicylate, and thiopurine use compared with the conventional approach.

EARLY INTERVENTION IN CD WITH OTHER BIOLOGIC CLASSES

Although there is mounting evidence that early use of anti-TNF agents leads to improved outcomes, the IBD biologic armamentarium is expanding. In addition to agents targeting TNF-alpha, anti-integrin (eg, vedolizumab) and anti-interleukin 12/23 (eg, ustekinumab) therapies are now available. Due to the favorable side effect profile associated with these newer agents, a positive outcome with earlier use may significantly impact their positioning. However, it is not clear that there is a similar pattern seen with disease duration when considering biologics that target inflammatory mediators other than TNF-alpha.

Anti-integrins (Vedolizumab)

The 2 anti-integrins currently available for use in CD are natalizumab and vedolizumab. Natalizumab was approved first, but its use has been limited due to concerns related to progressive multifocal leukoencephalopathy.[52] In the GEMINI 2[53] and GEMINI 3[54] trials for vedolizumab, clinical response and remission rates were higher among anti-TNF-naïve patients, providing indirect evidence for possible improved response with shorter disease duration; however, this question was not specifically analyzed.[55] More recently, in a real-world observational cohort of vedolizumab-treated patients, CD disease duration <2 years was significantly associated with higher rates of steroid-free clinical remission and endoscopic healing at 6 months.[56] Further data on the use of vedolizumab are needed to confirm this association and help with positioning of this biologic agent.

Anti-interleukin 12/23 (Ustekinumab)

Ustekinumab, a fully human immunoglobulin GI kappa monoclonal antibody that blocks the p40 subunit of IL-12/IL-23, is used as an induction and maintenance treatment for CD.[57, 58] In fact, it has been extensively studied after the failure of conventional therapy and anti-TNF agents. Therefore, its effect on patient outcomes when used as a firstline agent remains unclear. It is further uncertain whether disease duration has an impact on efficacy. Similar to the vedolizumab clinical trials, response rates were higher in anti-TNF-naïve patients treated with ustekinumab in the UNITI-2 trial compared with anti-TNF-exposed patients in UNITI-1.[58] When comparing the baseline characteristics of patients in both groups, the anti-TNF-naïve patients in UNITI-2 had a mean disease duration of 8.7 (±8.4) years, whereas the anti-TNF-exposed patients in UNITI-1 had a mean disease duration of 12.7 (±9.2) years. Although this difference is not within the range typically considered early CD,

it is indirect evidence that ustekinumab may work better in patients with shorter disease duration.

EARLY BIOLOGIC AGENTS IN UC

Unlike the studies investigating early use of biologic therapy in CD, there is minimal evidence suggesting the benefits of early aggressive therapy in UC, even with anti-TNFα agents. The benefit of early biologics in CD is to control inflammation and stave off progression to irreversible stricturing and penetrating disease. In contrast, UC patients have predominantly mucosal rather than transmural inflammation, and complications such as strictures remain rare.

EARLY INTERVENTION WITH ANTI-TNF AGENTS IN UC

Infliximab and Adalimumab

No post hoc analyses of clinical trials in UC have demonstrated a clear effect of disease duration on treatment response. Due to the paucity of data evaluating early anti-TNF therapy in UC, Ma et al. conducted a retrospective cohort study[59] to assess the effect of early initiation of infliximab or adalimumab in this patient population. Outcomes assessed included rate of colectomy, UC-related hospitalization, and secondary clinical loss of response during maintenance. Early initiation was defined as starting treatment within 3 years of diagnosis. In this study of 115 patients, 57 (49.6%) received early anti-TNF therapy, and the median time to treatment in this group was 38.1 weeks, compared with 414 weeks in the late initiator cohort. Results revealed that patients receiving early anti-TNF therapy had similar rates of colectomy, secondary loss of response, and UC-related hospitalizations compared with late initiators.

One of the main contributing factors for the above findings is that the UC patients starting early anti-TNF therapy had more active disease than the late initiators. For example, the mean endoscopic Mayo subscore at anti-TNF induction was 2.46 (±0.66) for early initiators compared with 1.86 (±0.67) for late initiators ($P < 0.001$). Additionally, the median CRP was also significantly higher in early initiators compared with late anti-TNF initiators (35.7 mg/L vs 6.4 mg/L; $P < 0.001$). It is well known that patients with severe UC are at risk for poor anti-TNF primary response and worse outcomes due to low albumin levels and accelerated fecal drug clearance.[60] Additionally, endoscopic disease severity is a powerful predictor of colectomy. Therefore, if early anti-TNF therapy had been initiated in those with lesser degrees of disease severity, perhaps a trend toward improved clinical and surgical outcomes would have been seen.

Other studies have similarly argued against early anti-TNF use in UC. In a retrospective cohort[61] of 213 steroid-refractory or steroid-dependent UC patients treated with infliximab, shorter UC duration at infliximab initiation predicted worse outcomes. In contrast, longer disease duration was associated with improved outcomes, including higher odds of 1-year steroid-free remission and a decreased risk of infliximab failure and colectomy. Another retrospective multicenter study by Oussalah et al. evaluated the short- and long-term outcomes of infliximab in UC and found that hospitalization rates were higher among patients with shorter disease duration (≤50 months; $P = 0.02$).[62] In the aforementioned study by Mandel et al., hospitalization rates decreased only in CD patients with early anti-TNF exposure (within 3 years from diagnosis), but not in patients with UC.[40] Even in the pediatric population, those with shorter UC disease duration (<20 months) before infliximab initiation had an increased likelihood for a colectomy within a year ($P = 0.04$).[63] Current data therefore suggest that disease duration has no impact on anti-TNF effectiveness in UC, and in fact risks of therapeutic failure may be higher in patients exposed to earlier biologic therapy.

EARLY INTERVENTION IN UC WITH OTHER BIOLOGIC CLASSES

Anti-Integrins (Vedolizumab)

In a post hoc analysis[64] of data from GEMINI 1, an analysis was performed to determine the effect of vedolizumab therapy in patients with UC based on their past exposure to anti-TNF agents. Results revealed that vedolizumab demonstrated significantly greater efficacy as induction and maintenance therapy for UC than placebo regardless of anti-TNF exposure. Nevertheless, there were numerically more treatment differences at week 6 among patients receiving vedolizumab who were naïve to TNF antagonists than patients with TNF antagonist failure. When comparing the baseline characteristics, the patients in the anti-TNF-naïve group had slightly shorter disease duration than those with anti-TNF failure. These findings, which are similar to the post hoc analyses performed in GEMINI 2 and GEMINI 3 in CD, reveal that vedolizumab may be a treatment option for early UC, perhaps even as a firstline biologic agent in those who are anti-TNF-naïve. More recent data, however, revealed that the impact of disease duration (≤2 years) on remission rates with vedolizumab was seen only in CD patients and not in those with UC.[56]

THE NEED FOR RISK STRATIFICATION

Inflammatory bowel disease continues to be a condition with a highly variable disease course. Some patients maintain mild manifestations of the disease, and others experience rapid disease progression. The goal of early treatment with biologic agents is to alter the natural history of the disease and prevent future complications. However, there is the risk of overtreatment in those with milder disease.[65] For example, patients with a more indolent disease course may not need early biologic therapy and would be unnecessarily exposed to these therapies. Therefore,

the ability to prognosticate at diagnosis which patients are more likely or unlikely to progress to disabling disease will aid in selection of candidates for early biologic treatment.

Certain clinical factors at diagnosis have been found to predict complicated CD with poor prognosis. For example, in a meta-analysis including 1961 patients, the clinical characteristics independently associated with higher risk of developing disabling disease included young age (<40 years) at diagnosis, initial requirement of steroids for treating the first flare, and perianal disease.[65, 66] A study by Zallot and Peyrin-Biroulet[67] defined complicated CD as the development of bowel damage (stricture, abscess, and/or fistula) and/or the need for surgery. Overall, using various definitions of complicated CD, the predictors of worse outcomes were extensive small bowel disease, rectal disease, perianal complications, early stricturing/penetrating disease, smoking, and young age at diagnosis.[67–70]

When considering the definition for complicated UC, Zallot and Peyrin-Biroulet included the need for colectomy, colon cancer, and extraintestinal manifestations.[67] In other studies, clinical risk factors for complicated UC included young age, male sex, extensive colitis, severe disease activity at diagnosis, primary sclerosing cholangitis, the need for steroids, and nonsmoking.[22, 65, 68, 71–74] Endoscopic severity (eg, deep ulceration) is considered to be a prognostic factor in both CD and UC, predicting the need for future surgery.[75–77]

Aside from clinical prognostication factors, various immunologic markers have been associated with a worse disease course, particularly for CD. The presence of antibodies against *Escherichia coli* outer-membrane porin C (OmpC), *Saccharomyces cerevisiae* (ASCA), flagellin (CBir1), and perinuclear antineutrophil antibody (pANCA) have been associated with fibrostenosing, internal penetrating small bowel disease, and need for early small bowel surgery.[65, 78–80] In a prospective study conducted in a large pediatric CD cohort, patients positive for at least 2 serological markers (ASCA, anti-OmpC, and/or anti-CBir1) progressed to internal penetrating and/or fibrostenosing disease faster than those positive for only 1 antibody. The group positive for all 3 antibodies demonstrated the fastest disease progression.[80, 81] In a Norwegian pediatric study,[82] the authors investigated the prevalence of serological markers in newly diagnosed treatment-naïve pediatric IBD patients and whether they were associated with early anti-TNF treatment. They found that the patients with early anti-TNF therapy had a significantly higher presence of antibodies against ASCA IgA and IgG and higher titers of ASCA compared with CD patients receiving conventional treatment. Conversely, CD patients with pANCA autoantibodies were less likely to receive early anti-TNF therapy. These findings suggest that pANCA-negative and/or ASCA-positive CD patients should be monitored more vigilantly with perhaps earlier aggressive treatment.

Other than serologic markers, certain genetic markers have also been shown to predict more aggressive disease. The IBD CHIP project[83] concluded that carriage of some NOD2 variants is an independent predictive factor for ileal CD, stricturing and penetrating behaviors, and the need for surgery. Other genetic markers including PRDM1 variants, IL23R, JAK2, and TNFS15 also appear to be associated with progressive, severe CD.[84] In a large Dutch CD cohort study,[85] Weersma et al. showed that an increased number of risk alleles at 5 risk loci (NOD2, IBD5, DLG5, ATG16L1, and IL23R) is associated with a more severe disease course. As for UC, previous studies have demonstrated that the HLA DRB1*0103 allele is associated with pancolitis and the need for colectomy.[86, 87]

It is well known that substantial morbidity is associated with IBD complications. Therefore, validated models that help identify risk of disease progression will allow for a more informed risk–benefit discussion regarding treatment. A visual web-based tool that takes into account a patient's clinical, serologic, and genetic data to provide a personalized risk profile has had promising results and may eventually be incorporated into clinical practice.[88]

ECONOMIC BURDEN WITH EARLY BIOLOGICS

A significant health care burden is associated with IBD in the United States. In 2009, IBD was the first-listed discharge diagnosis in >100,000 hospitalizations, a 37% increase from discharge diagnoses in 2000. These hospitalizations resulted in 569,918 total hospital-days, with a mean cost of $32,965 and aggregate costs of >$1 billion.[89] In 2010, the National Hospital Discharge Survey showed that the number of hospitalizations due to IBD more than doubled to 208,000.[90, 91] Although these numbers are high, hospitalizations make up only a portion of the total cost associated with IBD. For example, in 2014, IBD was estimated to result in direct and indirect US costs ranging from $14.6 to $31.6 billion.[92]

There is no debate that biologic therapy is expensive and that it is now the main driver of health care costs. US spending on prescription drugs increased by 4.8% to $323 billion from 2015 to 2016,[89] with increasing biologics as one of the main drivers for this spending growth. Biologics alone accounted for 38% of US prescription drug spending in 2015 (due to high cost per dose)[93] and for 70% of drug spending growth between 2010 and 2015.[94, 95]

Nevertheless, the cost of suboptimal therapy among IBD patients may be even more substantial. Each year, patients with UC and CD cost managed-care payers approximately $5066 and $8265, respectively. These costs are even higher in patients with suboptimal treatment, with estimates from health claims data (January 1, 2011, through December 31, 2013) at $12,679 for UC and $18,736 for CD.[90] With the increased use of biologic therapy and a push for earlier intervention, a shift has occurred, with the cost of medications replacing that of hospitalizations and surgical procedures. In a study investigating the impact of anti-TNF therapy on IBD-related expenditures, the proportion of anti-TNF-related health care costs increased over 2 years of follow-up, whereas hospitalization costs decreased.[90]

Aggressive biologic therapy early in the disease course allows for mucosal healing and can prevent progression to structural bowel damage.[77, 96] Several studies have further shown that biologic therapy leads to decreased complications, surgery, and hospitalization rates.[30, 53, 97–101] For these reasons, delays in initiating appropriate biologic therapy will lead to an increased risk of costly complications. Additionally, IBD often affects patients during their peak productive years, and remission will reduce indirect costs related to unemployment and absenteeism. It is therefore evident that despite the financial burden associated with these biologic agents, early initiation of such therapy should translate into lower long-term costs of treatment.[90]

Obstacles due to insurance

Many will agree that a "top-down" approach can lead to long-term savings. However, insurance companies have varying policies related to biologic therapy, and often mandate "step-wise" escalation. To assess whether insurance companies are compliant with current ideal practice guidelines, the National Association of Insurance Commisioners report was used to review the first 50 insurance companies with online policies regarding anti-TNF, vedolizumab, and ustekinumab therapies.[102] Step therapy was defined as the requirement by an insurance policy that a patient first try and fail 1 or more less expensive drugs before a more expensive drug is approved, regardless of disease severity. Results revealed that 98% of policies are inconsistent with the American Gastroenterological Association (AGA) UC care pathway and require step-wise drug failure before approval of an anti-TNF. Similarly, 90% of the policies were inconsistent with the AGA CD care pathway and required step-wise drug failure before approval of an anti-TNF. Twenty-eight percent required failure of at least 2 drugs (eg, corticosteroids, 5-ASAs, and/or thiopurines) before even considering an anti-TNF.[102]

The above study reveals that the vast majority of insurance companies in the United States require step-wise failure of drug therapy for both UC and CD, which is inconsistent with current guidelines. The plans do not allow for treatment based on disease severity. Only 2% of UC policies and 10% of CD policies allowed for early initiation of anti-TNF therapy. In addition, 34% of the policies required failure of at least 2 drugs before a biologic could even be considered. Waiting for less expensive medications such as corticosteroids to fail subjects patients to steroid-related toxicity and delays the opportunity to provide effective treatment. Additionally, why 26% of insurance companies required step-wise therapy for fistulizing CD, when infliximab is the only Food and Drug Administration–approved effective therapy for this complication, remains unclear. The reason—which is not directly stated but easily inferred—boils down to cost.[102]

Introduction of biosimilars

It is the hope that biosimilar entry into the pharmaceutical market will help decrease costs. As more biosimilars are introduced, competition is expected to drive prices down, reducing cost to patients and allowing greater access to biologic therapy. This will hopefully translate into earlier initiation of biologics in patients who would have otherwise waited for complications to arise. The European Union (EU) provides a preliminary impression of the effect biosimilar entry has had on the health care industry, with average list prices 30% lower than the reference product.[103, 104] Extrapolating to the American market, it is estimated that from 2017 to 2026, biosimilars will lead to a $54 billion reduction in direct biologic spending. This should translate into drastic savings for the American health care industry.[94]

CONCLUSIONS

The IBD treatment paradigm has been shifting from a conventional "step-up" approach toward a "top-down" early intervention treatment strategy. Unfortunately, the "step-up" strategy remains widely used in clinical practice (often forced by insurance companies) and leads to prolonged use of ineffective agents. This ultimately delays introduction of effective disease-modifying therapy and can result in progressive inflammation and irreversible structural bowel damage. The idea of a "window of opportunity," where introduction of biologic agents early in the disease course is most effective, has yet to become universally recognized.

Currently, the impact of disease duration is most lucid for anti-TNF agents in CD and is less clear with agents possessing divergent mechanisms of action. It is similarly unclear whether disease duration has an impact on efficacy of biologic therapy in UC. In fact, several studies have demonstrated worse outcomes with early biologic intervention in UC patients, which may be the product of confounding by indication. Further studies are needed to demonstrate a beneficial impact for early UC intervention or whether a rapid step-up approach remains sufficient. With the introduction of new biologics (eg, ustekinumab and vedolizumab) with a more favorable side effect profile, it will be interesting to see where these agents ultimately align in the IBD treatment algorithm.

Lastly, risk stratification at the time of diagnosis and creation of a universal system to predict disease progression will allow physicians to select the appropriate candidates for early biologic therapy.

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