

# Evolving Inflammatory Bowel Disease Treatment Paradigms: Top-Down Versus Step-Up

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## KEYWORDS

- Inflammatory bowel disease • Crohn disease
- Ulcerative colitis • Management • Anti-TNF • Biologic
- Therapy • Top-down

Crohn disease (CD) and ulcerative colitis (UC) comprise a group of inflammatory disorders of the gastrointestinal (GI) tract that can vary significantly in many aspects, including severity of disease, anatomic extent of inflammation, the presence and nature of extraintestinal manifestations, and response to therapeutic approaches.<sup>1-5</sup> This clinical heterogeneity has led to attempts at classifying CD based on the location and behavior of disease.<sup>6</sup> More recently, advances in understanding of genetic susceptibility to inflammatory bowel disease (IBD) suggest that CD and UC may represent a continuum of overlapping disorders,<sup>7,8</sup> which has led to an attempt to better classify IBD on clinical, molecular, and serologic grounds.<sup>9</sup> Beyond classification, differences in clinical, genetic, and immunologic profiles may require more targeted, refined treatment approaches based on more than disease location and severity. These approaches may help clinicians who make decisions in the rapidly evolving area of recently introduced biologic agents.

This article provides an overview of the current approaches to therapy for CD and UC. An in-depth review is beyond the scope of this article and can best be accomplished by referring to published guidelines.<sup>1,4,5,10</sup> This article focuses on the evidence supporting the rationale for changing paradigms in the management of IBD, including mucosal healing as an end point and earlier use of immunosuppressive and biologic agents, particularly in CD (so-called top-down therapy).<sup>11</sup> This review does not focus on the current controversy regarding concomitant immunosuppressive therapy versus

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monotherapy with the use of biologic agents. Although the majority of the proposed approaches outlined are based on the interpretation of evidence, some are reflective of the authors' opinion and may diverge from published guidelines.

### THE CHALLENGE OF CHOOSING THE APPROPRIATE THERAPY FOR THE NEWLY DIAGNOSED PATIENT WITH CD

The therapeutic approach to the patient with newly diagnosed CD is confounded by the clinical heterogeneity of the disease. The approach should differ based on the clinical presentation of the new patient. Patients presenting at diagnosis with a complicated disease phenotype, such as internal penetrating disease or perianal CD, are different from patients presenting with mild diarrhea and an ileocolonoscopy demonstrating scattered and superficial colonic aphthae. In considering initial therapeutic options, the clinician must consider the evidence that may point to differences in the history of an individual patient with CD.

CD is a chronic relapsing disease characterized by periods of apparent remission and obvious disease activity. Population-based data from Denmark have demonstrated that within a year of diagnosis more than 50% of patients are in remission, about one-third have highly active disease, and 15% have only mild disease.<sup>12</sup> A Markov model of a population-based inception cohort from Olmsted County, Minnesota, suggested a patient with CD would spend 24% of the time in medical remission on no medical therapy, 27% of the time being treated with mesalamine only, 41% of the time in postoperative remission, and only 7% of the time in a state requiring therapy with corticosteroids or immunosuppressants.<sup>13</sup> However, as discussed later in this article, the meaning of clinical or postoperative remission in the context of these studies and whether it is truly reflective of remission as it pertains to mucosal healing must be considered. **Similar to the heterogeneity of clinical presentation, the natural history of CD is equally diverse and the ideal is to have tools to aid in the prediction of a severe disease course versus a more indolent type of disease so that a more aggressive therapeutic approach can be instituted earlier instead of a more graduated approach.**

Several tools are available to the clinician that may aid in predicting a more aggressive course of disease in patients with CD. These include clinical, endoscopic, serologic, and genetic variables (a more expansive review is available in the article by Rubin in this issue). The most useful tools for clinicians are simple-to-use clinical predictors that can easily be applied in practice. **Clinical parameters, largely derived from retrospective studies, that predict a more aggressive disease course include a younger age of disease onset, active smoking, extensive small bowel disease, deep colonic ulcers, perianal disease, and an initial need for corticosteroids.**<sup>14-18</sup>

Other clinical factors that should be considered are extensive upper GI tract disease or disease of an undesirable location that would require extensive, complicated surgery. More recently, two commercially available panels of antibodies to microbial antigens have been associated with complicated small bowel disease behavior in adult and pediatric CD in cross-sectional and prospective studies.<sup>19-24</sup> These panels include antibodies directed at several microbial antigens including oligomannan (anti-*Saccharomyces cerevisiae* or ASCA), *Escherichia coli* outer membrane porin C (anti-OmpC), flagellin (anti-CBir1), antilaminaribioside (ALCA), antimannobioside (AMCA), antichitobioside (ACCA), antichitin (anti-C), and antilaminarin (anti-L).<sup>21,25-30</sup> The clinical utility of these panels is an area of ongoing interest, but their greatest potential may lie in their predictive capacity (for a more detailed review see the article by Rubin in this issue).

## THE CURRENT APPROACH TO MANAGING CD

Traditionally the goals of therapy have been to eliminate all symptoms related to a patient's CD. More recently, other goals have been advocated such as improving a patient's quality of life and reducing hospitalization, surgery, and mucosal healing. The means to achieve these goals may differ depending on the clinical presentation and presence or absence of extraintestinal manifestations of a patient's CD.

The standard therapies available to a clinician include 5-aminosalicylates, sulfasalazine, antimicrobial therapy, corticosteroids, immunosuppressive agents, and monoclonal antibodies (MAbs). The only commercially available MAbs include the three antitumor necrosis factor (TNF) antibodies, infliximab, adalimumab, and certolizumab pegol, and natalizumab, an MAb directed against the  $\alpha 4$ -integrin.<sup>31-35</sup> Therapy for CD should be thought of as acute or induction therapy, followed by maintenance therapy.

Induction therapy for patients with mild-to-moderate CD has traditionally consisted of 5-aminosalicylates or sulfasalazine or antimicrobial agents such as ciprofloxacin and metronidazole.<sup>36-46</sup> However, the evidence is clear that, with the possible exception of patients with mild colonic disease, these agents are ineffective and their routine use is not recommended.<sup>5,41,46,47</sup> Induction therapy with corticosteroids, however, is a highly effective strategy. Population-based studies demonstrate that after 30 days prednisone results in remission in 48% to 58% of patients, response in 26% to 32%, and lack of response in 16% to 20%.<sup>48,49</sup> Similar results were observed in a comparable cohort from the United Kingdom.<sup>50</sup> However, prolonged response occurs in only 32% to 44% and corticosteroid dependence occurs in 28% to 36%.<sup>45,46</sup> For patients with mild disease the systemic side effects of prednisone often do not warrant its use.<sup>51</sup> For patients who have mild-to-moderate CD that is limited to the ileum and right colon, controlled-release oral budesonide is a good option at a dose of 9 mg/d, which has been shown to be more effective than placebo or mesalamine at inducing response and remission and causes fewer corticosteroid side effects than systemic glucocorticoids.<sup>52-55</sup> Immunosuppressive agents such as azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX) have been studied for induction of active moderate-to-severe corticosteroid-dependent CD.<sup>56,57</sup> In a meta-analysis examining the use of AZA/6-MP, the odds ratio for response for active CD was 3.09; 16 weeks of parenteral MTX at a dose of 25 mg weekly led to remission in 39% of patients. However, neither agent is rapidly acting and they generally require concomitant corticosteroids for induction therapy. The only other therapeutic option associated with a rapid induction of response and remission is the anti-TNF $\alpha$  agents. Infliximab, adalimumab, and certolizumab pegol induction therapy is associated with response rates of approximately 40% to 80% at 4 to 12 weeks in patients for whom other standard therapies have failed.<sup>33,58-60</sup> Natalizumab was associated with sustained response and remission from weeks 4 to 8 in patients with an elevated C-reactive protein (CRP) in 48% and 26% of patients, respectively.<sup>35</sup>

Induction therapy serves to downregulate acutely the adaptive immune response that drives gut inflammation in CD. However, the underlying genetic and environmental predisposition remains unchanged, and hence maintenance therapy is generally required. Although the theoretical Markov model cited earlier in this article estimated that patients with CD would spend only 7% of their time in a disease state requiring immunosuppressive therapy or corticosteroids, this is in contrast to studies of actual patients. The data on short- and long-term response to corticosteroids found that a long-term response occurs in only 32% to 44% of patients and corticosteroid dependence occurs in 28% to 36%.<sup>48,49</sup> Data from a clinical trial comparing the use

of infliximab induction with AZA versus a more traditional approach of induction with corticosteroids followed by the addition of AZA on relapse (the top-down trial) found that at 52 weeks, 65% of patients had relapsed after corticosteroids and were eventually treated with AZA.<sup>11</sup> Therefore, the majority of patients with CD, particularly those treated with corticosteroid induction, require maintenance therapy. Fewer therapeutic agents are available for maintenance therapy than for induction therapy. Only the immunosuppressive agents (AZA, 6-MP, and MTX) and biologic agents have documented efficacy in the maintenance of response and remission in CD.<sup>31–33,56,61–63</sup>

Many clinicians still commonly apply a stepwise approach to the management of mild CD, using induction therapy with agents with limited systemic toxicity (eg, antimicrobials, mesalamine, or budesonide for ileal-right colonic disease) followed by maintenance therapy with an immunosuppressive agent after 1 or 2 episodes of symptomatic relapse,<sup>64</sup> particularly in patients who lack obvious clinical predictors of severe disease. In patients with moderate-to-severe CD, most clinicians would use systemic corticosteroids for induction therapy with the addition of an immunosuppressive agent concomitant with induction corticosteroids or after one symptomatic relapse.<sup>64</sup> In recent years, the use of immunosuppressive therapy has increased significantly.<sup>65</sup> **Biologic agents have traditionally been used only after failure of or intolerance to immunosuppressive therapy. In general, this escalating approach is referred to as “step-up therapy.”**

#### THE NATURAL HISTORY OF UC

UC has a heterogeneous course. Disease activity is generally described as mild, moderate, or severe, based on the number of bowel movements, presence and degree of rectal bleeding, and presence or absence of other systemic features.<sup>1</sup> Work from Denmark followed 1161 UC patients for 25 years and studied changes in disease activity.<sup>66</sup> This study found a rate of colectomy of 24% after 10 years of disease activity. Between the third and seventh year after diagnosis, 18% of patients had active disease on a yearly basis, 25% had persistent remission, and 57% had intermittent relapses. The only features that were found to be predictive of active disease course were the disease activity in the preceding years, the number of years with disease relapses, and the presence of systemic symptoms. A study from the same group, studying part of the same cohort, found that the disease location is not static.<sup>67</sup> Patients with proctosigmoiditis at diagnosis had a 53% likelihood of proximal extension within 25 years and, conversely, 75% of patients with pancolonic involvement developed less extensive overt disease during the same period. Discrepant from this study is a more recent Norwegian study of a 10-year follow-up of an inception cohort of UC patients, which found that proximal extension of distal disease occurred in only 20% of patients.<sup>68</sup> However, consistent with the Danish cohort, 83% of patients had a relapsing course and approximately one-half of patients were relapse free during the previous 5 years. The presence of pancolonic disease with an elevated erythrocyte sedimentation rate (ESR) was predictive of a higher likelihood of colectomy (which occurred in 9.8% of patients at 10 years). These studies show that UC is a heterogeneous disease in terms of location, extent, change over time, and disease course. Ability to predict disease course in UC is not so well developed as in CD.

#### THE CURRENT APPROACH TO MANAGING UC

The goals of therapy in UC are the same as those cited for CD. The therapies available to a clinician are identical to those that are available for CD, with a few key exceptions.

The anti-TNF agents adalimumab and certolizumab pegol and the anti- $\alpha$ ; 4-integrin natalizumab are not currently indicated for UC. Antimicrobial agents lack efficacy in UC and their use is not advocated.<sup>69,70</sup> Cyclosporine has proven efficacy in acute, severe UC.<sup>71,72</sup> Similarly, therapy should be thought of as induction and maintenance therapy.<sup>4</sup>

Induction therapy for mild-to-moderate UC generally consists of 5-aminosalicylate therapy (sulfasalazine or mesalamine), which, unlike CD, is a highly effective strategy.<sup>4,73,74</sup> Approximately 40% to 80% of patients will respond within 4 weeks to orally administered 5-aminosalicylates.<sup>4,73,74</sup> Many of the symptoms of UC, such as urgency and tenesmus, arise from rectal inflammation. The optimal approach to therapy, regardless of the extent of disease, is combined oral and rectal aminosalicylates.<sup>75,76</sup> For those patients who do not initially respond to 5-aminosalicylates or who have more severe symptoms, corticosteroids are an effective induction therapy. Population-based data from Olmsted County, Minnesota have demonstrated that at 30 days, 54% of patients achieve complete remission, 30% achieve partial remission, and 16% fail to respond.<sup>49</sup> At 1 year, 49% maintain response, 22% are corticosteroid dependent, and 29% go on to require colectomy. Therefore, the requirement for a course of corticosteroids in UC can also be seen as a bad prognostic indicator. As in CD, the use of 6-MP/AZA in UC requires a significant time of onset; these are not good inductive agents and usually require concomitant use of corticosteroids. The role of these agents is less clear than in CD because there is considerable heterogeneity in study design. A recent meta-analysis evaluated the use of 6-MP/AZA for induction of remission in UC and, using a pooled analysis of 4 studies that met inclusion criteria, found an odds ratio of 1.59 favoring 6-MP/AZA, but the confidence interval was not significant (0.59–4.29).<sup>77</sup> This pooled analysis of 4 studies included a total of only 89 patients, reflecting the small nature of many of the studies evaluating these agents in UC. The only other agent with well-documented efficacy in inducing remission in UC is infliximab. In the active ulcerative colitis trial (ACT) 1 and ACT 2 trials for moderate-to-severe UC, the use of 5 mg/kg of infliximab induction therapy was associated with a 67% response rate and a 36% remission rate at 8 weeks in patients who had active disease despite standard therapies (aminosalicylates, corticosteroids, or 6-MP/AZA).<sup>78</sup> Maintenance of response and remission can be achieved in UC with 5-aminosalicylates, 6-MP/AZA, and infliximab.<sup>4,78,79</sup> Similar to induction studies, the PEGylated antibody Fragment Evaluation in Crohn Diseases Safety and Efficacy (PRECISE) role and efficacy of 6-MP/AZA is unclear, although a recent meta-analysis including 4 studies and 232 patients found a significant odds ratio favoring 6-MP/AZA over control. A clinical trial evaluating AZA versus infliximab versus combination therapy with both agents in patients naive to these therapies for induction and maintenance of UC is ongoing and may clarify the role of these agents in UC.

#### **WHICH IS THE BETTER WAY TO DETERMINE RESPONSE TO THERAPY IN IBD: SYMPTOMS OR ENDOSCOPIC ASSESSMENT?**

In clinical practice, the assessment of disease activity in UC and CD has traditionally been accomplished by assessing clinical symptoms such as the presence or absence of blood, the number of stools per day, and the presence or absence of evidence of systemic toxicity. In addition, other means such as elevation in the ESR or CRP can be useful.<sup>80,81</sup> More recently, fecal markers such as fecal calprotectin have shown significant promise.<sup>82</sup> In clinical trials, investigators rely on activity indices that are highly symptom based, such as the Crohn Disease Activity Index (CDAI) or Harvey-Bradshaw Index (HBI) in CD, and the Mayo score, among others, for UC.<sup>83–85</sup>

Patients with IBD often have symptoms that are not related to inflammatory lesions of the GI tract. Symptoms can have many causes, including medication side effects, choleric diarrhea after ileal resection in CD, and postsurgical diarrhea. Many patients with IBD will develop a syndrome of postinflammatory irritable bowel that is not reflective of demonstrable inflammation at a mucosal level, which may explain the high placebo response rates that have been seen in some clinical trials evaluating the use of biologic agents for CD.<sup>34,60</sup> Subsequent stratification of patients by more objective evidence of inflammation, such as elevated CRP, has demonstrated efficacy among patients with active inflammation versus lack of efficacy in those who probably lack significant inflammation.<sup>35,60</sup> With the more recent practice of incorporating mucosal assessment into clinical trial protocols, this efficacy can be demonstrated even more clearly. In the Study of Biologic and Immunomodulator Naive Patients in Crohn Disease (the SONIC study), evaluating AZA, infliximab monotherapy, and infliximab in combination with AZA for patients with active CD who were naive to both classes of medications, there was strong evidence for the superiority of infliximab alone or in combination with AZA in patients with mucosal lesions at baseline, but no difference in efficacy in patients who lacked mucosal lesions at baseline but still qualified based on CDAI.<sup>86</sup> CDAI has been shown to lack correlation to the presence and degree of endoscopic lesions in CD.<sup>80</sup> This demonstrates that relying on clinical symptoms alone when making key therapeutic decision is fraught with difficulty and represents an error-prone approach to management.

The disconnect between mucosal lesions and symptoms is illustrated by studies of postoperative recurrence of CD. Within a year after intestinal resection, at least 70% of patients have recurrent disease endoscopically, yet clinical recurrence occurs in only one-third by 3 years, implying that endoscopic lesions and symptoms may not correlate.<sup>87-90</sup> A recent study, presented in abstract form, demonstrated that determination of the clinical impression of disease activity had a sensitivity and specificity of only 56.4% and 80.9%, respectively when compared with colonoscopy as the gold standard.<sup>91</sup> In clinical trials of mesalamine and infliximab for UC, endoscopic healing has been demonstrated to exceed the proportion of patients meeting criteria for clinical improvement or remission, emphasizing that noninflammatory processes can drive symptoms in IBD.<sup>78,92</sup> This led to attempts at developing disease activity indices that are more comprehensive and take into account not only clinical symptoms but also noninvasive markers of inflammation such as fecal lactoferrin.<sup>93</sup>

## THE VALUE OF MUCOSAL HEALING AS AN END POINT IN IBD

The notion that mucosal assessment is a more representative means of assessing disease activity is important, but more important is the relevance of achieving such an end point. Healing of mucosal ulceration should be a superior strategy to achieving clinical remission or improvement alone in the presence of persistent mucosal lesions. However, until recently, there was not much evidence to support such an intuitive assertion.

Data from a large Norwegian population-based cohort of incident UC and CD patients provides insight into the value of achieving mucosal healing.<sup>94</sup> Of 740 patients in the cohort, baseline and repeat endoscopic assessment was available in 495. In UC patients, the presence of mucosal healing 1 year after diagnosis was significantly associated with a reduced need for colectomy at 5 years. In patients with CD, the presence of mucosal healing at 1 year was associated with reduced subsequent need for corticosteroids. In addition, there was a numerical, but not a statistical, reduction in the need for surgery. Mucosal healing at 1 year in CD was associated

with mucosal healing at 5 years. This incident cohort spanned 1990 to 1994, before the advent of biologic agents, and signifies that the achievement of mucosal healing by any means is valuable and is not reflective only of the effect of biologic agents.

There are important data about the advantages of achieving mucosal healing in the specific context of biologic agents. Data from the ACCENT-I (A Crohn Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) trial for infliximab demonstrated that patients on infliximab who achieved mucosal healing tended toward lower rates of hospitalization.<sup>95</sup> More recent longitudinal data from a large cohort of CD patients in Leuven demonstrates that the presence of mucosal healing during therapy with infliximab was strongly associated with a lower risk of major abdominal surgery.<sup>96</sup>

Data should be examined with respect to the ability of the available therapeutic agents in terms of inducing mucosal healing, as this is likely to be better reflective of their true efficacy.

In IBD, mucosal healing data are available for corticosteroids, AZA/6-MP, MTX, infliximab, certolizumab pegol, and adalimumab.

Mucosal healing data for corticosteroids are limited and the definition of mucosal healing in older studies is markedly less rigorous than by current defined endoscopic scoring systems. In CD and UC, the use of corticosteroids has not been associated with significant degrees of mucosal healing.<sup>97,98</sup> A more recent study using a more contemporary definition of mucosal healing compared AZA with budesonide for patients with ileal or ileocolonic CD and budesonide was associated with complete or near-complete mucosal healing in only 24% of patients.<sup>99</sup>

Until recently, there were limited data regarding mucosal healing with the use of mesalamine in UC. However, with the recent development of Multi-Matrix System (MMX) mesalamine, there are mucosal healing data from trials in UC.<sup>73,74</sup> At 8 weeks, approximately 35% to 40% of patients on 2.4 to 4.8 g/d of MMX mesalamine achieved mucosal healing in 2 pivotal trials of this agent. There are no mucosal healing data for mesalamine in CD.

Data for AZA/6-MP come from two lines of evidence: postoperative prevention studies and a recent prospective randomized controlled trial for active CD.<sup>86,100,101</sup> Postoperative prevention studies have been inconsistent and largely disappointing. An open-label randomized trial of 2 mg/kg/d of AZA versus 3 g/d of mesalamine failed to demonstrate a difference in clinical recurrence at 24 months, but there was no endoscopic component to this study.<sup>100</sup> A later study evaluating 50 mg/d of 6-MP versus mesalamine and placebo demonstrated a lower endoscopic recurrence rate with 6-MP compared with placebo, but the endoscopic recurrence rate at 24 months with 6-MP was still 43%.<sup>101</sup> The best and most informative data regarding the efficacy of AZA in induction of mucosal healing come from the SONIC trial mentioned earlier in this article that evaluated AZA versus infliximab versus infliximab in combination with AZA in patients with active CD, naive to infliximab and AZA, requiring corticosteroids to control symptoms.<sup>86</sup> As discussed later in this article, the rate of mucosal healing at 26 weeks was only 16.5% with AZA. There are no mucosal healing data for AZA in UC, although a study similar in design to the SONIC trial is ongoing.

There are few data regarding mucosal healing with the use of MTX. One small pilot study in patients with CD and UC and a second small study published only in abstract form suggested some ability to induce healing of mucosal lesions but more data are needed.<sup>102,103</sup>

The data for mucosal healing in CD with infliximab are discussed in detail later in this article. Recently, data have been published in abstract form regarding mucosal healing in CD with certolizumab pegol and adalimumab.<sup>104,105</sup> In a prospective trial

135 patients were randomized to either adalimumab induction therapy (160 mg/80 mg) followed by 40 mg every other week, or induction alone followed by placebo for 52 weeks. Adalimumab induction and maintenance were associated with complete mucosal healing at 52 weeks in 24.2% versus 0% in patients induced but not maintained on adalimumab. In an open-label study, patients were treated with 400 mg of certolizumab pegol at 0, 2, and 4 weeks and then every 4 weeks up to week 54. Endoscopic remission as defined by the Crohn Disease Endoscopic Index of Severity was noted by week 10 in 55.1% of patients, but complete mucosal healing (a more stringent end point used in the infliximab and adalimumab data) occurred in only 6.1% of patients. In UC, infliximab, 5 mg/kg induction and maintenance were associated with an approximately 45% to 50% rate of mucosal healing at week 30 in the ACT 1 and ACT 2 trials evaluating this agent for induction and maintenance of moderate to severe UC (defined as an endoscopy subcore of 0 or 1).<sup>78</sup> There are currently no mucosal healing data for adalimumab or certolizumab pegol in UC and neither agent is currently indicated for this disease. Studies with adalimumab are ongoing.

#### WHAT IS THE RATIONALE FOR TOP-DOWN THERAPY IN CD?

There is mounting evidence that a strategy of earlier use of more potent immunosuppressive therapies may be the optimal approach to therapy in properly selected patients. The key to understanding this lies in the natural history of CD, particularly that of small bowel disease and those patients who require corticosteroids. In a retrospective study of more than 2000 patients with CD, the long-term evolution of disease behavior was investigated.<sup>106</sup> Patients progress in a stepwise fashion from inflammatory lesions (likely most amenable to therapy) toward irreversible structural disease such as strictures and penetrating disease. Antiinflammatory therapy presents a limited opportunity for treatment. A direct analogy can be made with inflammatory joint disease, in which irreversible structural damage occurs early and rapidly and may not necessarily be related to symptoms. Rheumatologists have used immunosuppressive therapy early in the course of rheumatoid arthritis and more recent data suggest that the early introduction of anti-TNF agents not only slows or halts progression of structural damage but may also allow the eventual withdrawal of immunosuppressive therapy.<sup>107,108</sup>

Although the historical standard in terms of a treatment approach to treating UC and CD has been a stepwise process as described earlier in this article, this uniform approach has failings that put patients with a high likelihood of progressive disease at risk. There is a process by which biologic agents, specifically TNF $\alpha$ ; antagonists, are used as the initial induction therapy, and this therapeutic paradigm has been referred to as a top-down strategy. There is compelling evidence to substantiate this approach.

The first example of top-down therapy may have been a randomized, placebo-controlled trial of 6-MP and prednisone in pediatric patients with newly diagnosed CD published by Markowitz and colleagues.<sup>109</sup> Patients were randomized within 8 weeks of diagnosis to 6-MP 1.5 mg/kg/d plus a tapering course of prednisone versus placebo and prednisone. Maintenance therapy with 6-MP or placebo was continued for 18 months. Remission was achieved in 89% of patients overall, but in patients maintained with 6-MP, the 18-month relapse rate was only 9% versus 47% in those maintained with placebo ( $P = .007$ ). Those patients treated with 6-MP were exposed to a lower cumulative dose of corticosteroids. Although in the current paradigm initial

use of an immunosuppressive agent such as 6-MP would not be considered top-down, that study represented at the time a departure from traditional practice.

The next evidence comes from retrospective analyses of large randomized controlled trials of the anti-TNF agents adalimumab and certolizumab pegol. In the Crohn Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (the CHARM trial), which evaluated maintenance of response and remission to adalimumab, the week-26 rate of maintenance of remission with adalimumab 40 mg every other week was 56% in patients with a disease duration less than 2 years, 35% in those with a disease duration of 2 to 5 years, and 37% in those with disease longer than 5 years.<sup>110</sup> In the PRECISE 2 study evaluating maintenance of response and remission with certolizumab pegol in CD, 62% of patients maintained response at week 26.<sup>63</sup> However, in those with an elevated CRP and a disease duration of less than 2 years, the maintenance of response was 90% ( $P = .02$ ), suggesting that early use of an anti-TNF agent was more successful.<sup>111</sup> Although comparing clinical trials of differing designs and with different patient populations should be discouraged, some insight can be drawn from a comparison of the ACCENT-I trial evaluating induction and maintenance of response and remission with infliximab for adult CD and the Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF $\alpha$ ; Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe Crohn Disease (REACH) trial evaluating infliximab in pediatric patients.<sup>31,112</sup> The median disease duration in ACCENT-I was approximately 8 years, whereas in REACH it was approximately 2 years. The week 10 and 54 response rates in REACH were 88.4% and 63.5% versus 70% and 43%, respectively for the same time points in ACCENT-I.

The most compelling data in support of the top-down strategy come from prospective studies of patients with newly diagnosed CD naive to all therapy apart from mesalamine or antibiotics (the top-down trial), and in relatively newly diagnosed CD naive to biologic agents and immunosuppressive therapy (SONIC) and patients who have undergone ileocecal resection for CD.<sup>11,86,113</sup>

In a randomized control trial of patients with newly diagnosed CD who were naive to corticosteroids, immunomodulators, and anti-TNF $\alpha$ ; agents, treatment was initiated as a top-down approach with infliximab 5 mg/kg at weeks 0, 2, and 6, and AZA 2.5 mg/kg/d with infliximab being delivered subsequently on an episodic, as-needed schedule or as a more traditional step-up approach with corticosteroids followed by the initiation of AZA on relapse or in cases of corticosteroid dependence, only then to be followed by infliximab in cases of ongoing disease activity.<sup>11</sup> The primary end point was clinical remission without corticosteroids and without surgery at weeks 26 and 52. At weeks 26 and 52, 60% and 62%, respectively of patients treated with early infliximab met this end point versus 36% and 42%, respectively in the step-up group. The trial demonstrated that active CD could be treated without using corticosteroids. At 104 weeks, there was no longer a difference between the two groups in terms of clinical remission. However, in patients treated with early infliximab, the rate of mucosal healing at 104 weeks was 71% versus only 30% in patients treated in a conventional step-up manner. The achievement of mucosal healing at 2 years was a strong predictor of remission from steroids, absence of subsequent relapse, or need for further anti-TNF therapy up to follow-up of 4 years, implying that early, aggressive therapy could have long-term benefits,<sup>114</sup> despite the trial design of episodic use of infliximab rather than regularly scheduled therapy, which is now advocated. The results might have been even more compelling had patients been on further maintenance therapy with infliximab, which is a subject in need of further study.

Although the SONIC trial is not strictly top-down, it provides similar insight into the advantage of earlier use of an anti-TNF agent. The median disease duration in the SONIC trial was just more than 2 years. Patients with active CD requiring corticosteroids were randomized to AZA 2.5 mg/kg/d, infliximab 5 mg/kg induction and maintenance, or the combination of both agents. The primary end point was remission from corticosteroids at week 26, but important secondary end points included mucosal healing at week 26 and pharmacokinetic data on infliximab levels and antibodies to infliximab. At 26 weeks, 30.6% of patients on AZA were in remission from corticosteroids compared with 44.4% with infliximab monotherapy and 56.8% for those on combination therapy with both agents. Mucosal healing at the same time was even more striking at 16.5% with AZA, 30.1% with infliximab monotherapy, and 43.9% with combination therapy.

The ultimate top-down therapy is to initiate treatment before the development of disease. Although this is impossible at present, a rough approximation of this model is the paradigm of prevention of surgically induced remission, before the development of recurrent mucosal disease. There is an insight into the benefit of anti-TNF $\alpha$  therapy in this setting in the context of a small randomized controlled trial of 24 CD patients comparing postoperative infliximab induction and maintenance therapy to standard postoperative therapy. At 1 year, infliximab induction and maintenance were associated with a 9.1% rate of endoscopic recurrence versus 84.6% with placebo. Of the placebo-treated patients, 53.8% were on immunosuppressive therapy during the trial.

This evidence unequivocally demonstrates several key points. Intervention earlier in the course of disease with effective therapy is likely to be more successful. This type of early intervention may decrease the likelihood of disease progression to more aggressive phenotypes that require surgical intervention. Anti-TNF agents appear to be more successful in patients with shorter duration disease and, at least for infliximab, are markedly superior to AZA at inducing mucosal healing. Achieving early mucosal healing appears to have long-term benefits that may truly alter the natural history of a patient's CD. From a health economic perspective, a top-down approach was studied using administrative claims data, which have been presented in abstract form.<sup>115</sup> Rubin and colleagues studied the claims data for more than 3000 CD patients who were treated with biologic agents. A step-up approach was identified if the biologic agent followed other therapies and a top-down approach was identified if a biologic agent was initiated within 30 days of diagnosis of CD. Those patients treated with biologic agents earlier were noted to have a lower rate of CD-related surgery. Although the study did not investigate costs directly, this is likely to be a less expensive strategy.

## IS THERE RATIONALE FOR TOP-DOWN THERAPY IN UC?

Unlike CD in which longer duration of disease is associated with a higher likelihood of irreversible structural damage, the same cannot be said of UC. One important long-term issue with UC is the development of dysplasia, for which the presence of unchecked inflammation is a key risk factor.<sup>116</sup> Theoretically, therefore, earlier use of an agent known to exert a potent biologic effect and lead to mucosal healing could have a long-term benefit. However, the best evidence for prevention of dysplasia currently exists for 5-aminosalicylates, and similar evidence is lacking for infliximab.<sup>117</sup> A subanalysis of the ACT 1 and ACT 2 trials failed to demonstrate any difference in response rates to infliximab with patients with disease duration of less than 3 years versus greater than 3 years.<sup>118</sup> Therefore, at present, there is little rationale for a top-down approach to managing UC. There will be patients who will have an

accelerating disease course and would likely benefit from earlier intervention, but the current tools do not allow reliable advance identification of these patients. Further study is needed in this area of IBD management.

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## THE FUTURE APPROACH TO THE MANAGEMENT OF IBD

The future management approach to IBD will be based on accurate and detailed phenotype and risk assessment at diagnosis based on clinical, serologic and genetic profiling. Those patients with a global risk that puts them at higher likelihood of rapidly progressive disease and the development of disabling complications should be treated with the most effective therapy as early as possible (currently anti-TNF $\alpha$ ; agents). Similar arguments can be made to use a top-down approach with anti-TNF $\alpha$ ; agents in CD patients with disease of an undesirable time span or location. It still remains a point of debate whether a biologic agent needs to be combined with AZA initially, although this has clearly been demonstrated to be superior in efficacy in the SONIC trial. Conversely, patients with a lower risk profile can be managed with a more traditional stepwise approach. Paramount to both treatment paradigms, however, is use of tools for the assessment of mucosal disease as the key measure of response, given the clear evidence that this is most reflective of disease activity and is most predictive of long-term success.

This approach is nearing realization in CD given the advances in understanding of genetics of this disorder, but more work is clearly needed in UC.

If a top-down approach is adopted by clinicians, several critically important questions remain. Does top-down therapy and successful induction of mucosal healing require an ongoing maintenance biologic or can it be withdrawn? Will this approach truly alter the natural history of CD in the long-term, or simply delay complications? Will this approach reduce the number of hospitalizations and operations universally? Will this approach be safe? Each answer leads to new questions but it is clear that the management of IBD in the 21st century will continue to evolve and unprecedented progress seems imminent.

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