Traditionally, inflammatory bowel disease (IBD) has been divided into 2 distinct entities: ulcerative colitis (UC) and Crohn’s disease (CD). A nuanced view presents IBD as an immunoinflammatory spectrum of chronic and recurring diseases of the intestines. This newly gained perspective holds the promise of moving treatment in a more proactive, personalized direction—toward targeting molecules and assessing risk, rather than treating symptoms.

The greatest challenge for clinicians who treat patients with IBD is to move from symptom-oriented (step-up) strategies toward prevention-oriented (early intervention) strategies aimed at altering the natural history of IBD. This review focuses on the treatment of IBD with 5-aminosalicylic acid (5-ASA) agents and contrasts conventional and novel (early intervention) approaches in patients who do not respond to 5-ASA therapy.

Challenging the Traditional IBD Diagnosis

One of the major questions facing clinicians is whether the disease is a single entity or a spectrum of multiple disorders. This distinction becomes particularly difficult to make when attempting to classify CD. Three distinct manifestations of CD have been described—inflammatory, fistulizing, and fibrostenotic. However, Crohn’s colitis has not been well defined in the literature. Some patients present with CD-like features—such as UC with rectal sparing or UC with nonpneumatoid granulomas. Other manifestations of the heterogeneity of colitis are a superficial mucosal CD involving left-sided refractory colitis with rectal involvement that may actually represent a type of mixed collagenous colitis or vascular collagen disorder still undefined, rectal disease...
with cecal patch, and a form of UC with post-treatment alterations.\textsuperscript{5}

The many forms of UC (ulcerative proctitis, left-sided colitis, and universal colitis) led Brooke\textsuperscript{6} to suggest that, rather than a single disease entity, UC represents a pathologic state with many etiologies. Indeterminate colitis (IC) might represent part of an immunologic continuum, rather than a well-defined clinical subset of UC and CD.\textsuperscript{5,6} IBD is not an autoimmune disease; it is a dysregulated immune response to luminal microbial antigens. Serologic markers may provide a window for observing an abnormal antibody–antigen response and may help identify patients at risk for rapid progression of disease who may benefit from early intervention.\textsuperscript{7} Molecular diagnostics, such as antibody serology and biomarkers, hold the promise of enhancing the understanding of IC and stratifying patients with IBD on the basis of immunophenotypes.

Differential diagnosis is increasingly recognized as important in distinguishing active inflammation from medication-pseudorefractory IBD, which may include infections (eg, \textit{Clostridium difficile}, cytomegalovirus), overlap with irritable bowel syndrome, celiac disease, lactose and/or fructose intolerance, dietary indiscretion, bile acid diarrhea, and obstructive stricturing or fistulizing CD requiring surgery) and in stratifying optimal therapeutic response to biologics and immunosuppressives.\textsuperscript{8} In select patients with moderately to severely active IBD, early intervention with effective therapy is associated with significant improvement in mucosal healing and reduction in the progression of disease.\textsuperscript{9,10}

**Molecular Classification of IBD**

IBD nomenclature does not accurately reflect the complexity of clinical phenotype. Although the role of serum antibody markers remains controversial, using a combination of markers enhances accuracy and specificity in classifying IBD-related aberrant immunophenotypes. The emerging role of molecular diagnostics is vital in characterizing the immunologic heterogeneity of IBD, and will be a bridge linking clinical immunophenotypes with genotypes.\textsuperscript{11,12} While new genes continue to highlight host microbial interactions,\textsuperscript{13,14} serologic markers indicate dysregulated antibody-antigen immune responses.

Differentiation between types of IBD becomes important in stratifying therapeutic strategies. Poor therapeutic response is an indication for surgery in nearly 29% to 30% of patients with UC and approximately 50% to 70% of patients with CD. Patients with refractory left-sided colitis or IC may benefit from serologic testing, in addition to documentation of clubbing and oral aphthae.\textsuperscript{15} In these patients, if the markers are more consistent with a molecular pattern of CD, physicians may consider anti-tumor necrosis factor (TNF) therapy as an option rather than total colectomy.

Serologic profiling already has proven helpful in patient stratification. Although controversial, high levels of perinuclear antineutrophil cytoplasmic antibodies (pANCA) have consistently correlated with postoperative pouchitis.\textsuperscript{16} Anti-CBir1 is an antibody to flagellin of the \textit{Clostridium} species; anti-CBir1 is associated with an increased incidence of chronic pouchitis in patients who have high pANCA levels, and with acute pouchitis in those with low pANCA levels.\textsuperscript{16} Expression of anti-Saccharomyces cerevisiae antibody (both immunoglobulin [lg] subtypes A and G) correlates with a younger age of onset and more aggressive fibrostenotic disease.\textsuperscript{17,18} Additionally, antibodies against the CD-related bacterial sequence I2, \textit{Escherichia coli} outer membrane porin C, and CBir1 flagellin identify a unique subset of immunologically vulnerable patients with complicated/aggressive CD.\textsuperscript{19,20}

Serologic diagnostic and biomarker testing provides a molecular snapshot of patients with IBD. New markers and prospective trials are required to correlate immunologic, molecular, and clinical patterns of IBD and will advance the risk assessment of patients, the selection of prevention-oriented therapies, and the science of IBD.

**Treatment of IBD Subtypes**

The majority of patients with IBD have moderate disease. Three-fourths of patients have active UC,\textsuperscript{21} and two-thirds of patients with CD have moderate to severe disease that requires alternatives to treatment with mesalamine therapies.\textsuperscript{22} The treatment goals for patients with IBD are universal: induce remission as quickly as possible, maintain remission as long as possible, facilitate mucosal healing, improve quality of life, minimize toxicity, and minimize cost.

For patients with UC, oral and rectal 5-ASA agents (including free 5-ASA and 5-ASA prodrugs), corticosteroids (IV [eg, hydrocortisone] or oral [eg, prednisone, methylprednisolone]), immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP]), and cyclosporine are used to induce remission. For maintenance of remission of UC, 5-ASAs and 6-MP, or AZA may be used. Additionally, infliximab is approved for the reduction of signs and symptoms, induction of clinical remission and mucosal healing, and elimination of corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapies.\textsuperscript{23}

For patients with CD, 5-ASAs, antibiotics (eg, metronidazole, ciprofloxacin [alone or in combination]), corticosteroids (including topically active, rapidly metabolized budesonide), immunomodulators (eg, 6-MP, AZA, methotrexate [MTX]), and infliximab are used to induce remission. For maintenance of remission, 5-ASAs, antibiotics, immunomodulators, and infliximab can be used. Most recently, the anti-TNF agents adalimumab and certolizumab have been approved for the induction and maintenance of clinical remission in adult patients with moderate to severe CD who have had an inadequate response to conventional therapies and for the induction of remission in those patients who also have lost response to or are intolerant to infliximab.\textsuperscript{24-29}
Probiotics and novel antibiotics (eg, rifaximin) have the potential to revolutionize the treatment of patients with IBD. For example, anti-inflammatory interleukin (IL)-10 levels have been associated with *Bifidobacterium infantis*. However, a greater understanding of gut microbiology and further clinical trials are needed.

**IBD in the Pregnant Patient**

Female patients who are contemplating pregnancy should be reminded that the goals for treating IBD during pregnancy are similar to those for treating nonpregnant patients with IBD: to induce and maintain steroid-free remission with control of inflammation and to promote durable mucosal healing. During pregnancy, the risks for toxicity from medication need to be balanced in the context of the risk for active, ineffectively treated IBD. For both pregnant and non-pregnant patients, active ineffectively treated IBD poses a greater overall risk than the toxicity of IBD medications.

Increasingly, young patients are evaluating the risk associated with initiating immunosuppressives and biologics earlier in the course of disease compared with long-term exposure to steroids. Some patients are interested in moving away from a symptom-oriented approach to disease management toward disease-prevention strategies. They are interested in therapies that prevent the progression of CD to structural damage (ie, stricturing and fistulizing disease) and that of colitis to dysplasia and colitis-associated colorectal cancer. Patients also are increasingly aware of the impact of nutrition (including vitamin D) on disease course and the risk for osteoporosis.

The Piano Registry, a prospective study of women with IBD, showed that fewer developmental milestones were met by infants at month 9 whose mothers were exposed to AZA/6-MP compared with infants whose mothers were exposed to biologics or who were not exposed to medications. There was no increase in adverse pregnancy outcomes in either of the treatment groups compared with the unexposed group.

**5-ASA: First-Line Therapy**

**Mechanisms of Action**

The specific goals of 5-ASA therapy are to quickly induce complete remission, facilitate mucosal healing, and minimize steroid use and toxicity. One proposed mechanism of action of 5-ASA is the inhibition of the cyclooxygenase (COX) and 5-lipoxygenase pathways of arachidonic acid metabolism, resulting in a decrease of proinflammatory prostaglandins and leukotrienes. The role of the COX pathway and prostaglandin biosynthesis in IBD remains to be elucidated. Attention has shifted from the arachidonic acid cascade to nuclear factor-kappa B (NF-κB). The discovery of the role of nucleotide-binding oligomerization domain 2 in the activation of NF-κB emphasizes the importance of NF-κB in the inflammatory signaling cascade and its interaction with luminal bacterial antigens and genetic susceptibility.

In vitro studies demonstrate that sulfasalazine inhibits NF-κB, which provides evidence in support of the direct biologic efficacy of 5-ASA. Clinicians should question whether the site of 5-ASA release is a determinant in optimizing and individualizing therapy. Two therapeutic strategies expose opposing views: One is that all 5-ASA preparations are equivalent; the other is that subtle differences in the mode of 5-ASA delivery translate into differences in clinical efficacy. Often overlooked is the distribution of UC; more than 50% of patients have left-sided disease (Figure 1). Both mesalamine (free, un conjugated 5-ASA) and mesalamine prodrugs (azo-bonded 5-ASA) have similar modes of action. Sulfasalazine, the archetypal azo-bonded 5-ASA designer drug, is engineered to release free 5-ASA (mesalamine) in the colon, protecting it from proximal absorption. Intolerance and hypersensitivity to the sulfapyridine moiety limit the dose of sulfasalazine, and have led to the development of new 5-ASA-containing analogs. The newer topical and oral 5-ASA agents are delivered to different anatomic sites, ideally corresponding to the distribution of active disease (Figure 2; Table). Although these agents are less toxic than sulfapyridine, mesalamine allergies and intolerance may occur, and interstitial nephritis has been reported with the 5-ASA moiety alone. Although rare, the potential for this adverse event (AE) mandates periodic renal function monitoring.
Table. Mechanisms of Release of 5-ASA–Containing Drugs

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Advantage</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>Diffusion-dependent</td>
<td>Time-released, moisture-dependent ethylcellulose-encapsulated mesalamine travels in solution and allows free 5-ASA mesalamine to diffuse out of the ethylcellulose beads and begin releasing in the upper intestines and continue throughout the small and large intestines.</td>
<td>Independent of pH or bacteria; mucosal delivery of mesalamine is less affected by rapid intestinal transit time (ie, diarrhea).</td>
<td>Free 5-ASA (mesalamine) is indicated in patients with proximal disease activity, severe diarrhea, strictures (1-mm ethylcellulose microspheres offer advantages), pouchitis (the constant moisture-dependent release may provide advantages), and postoperative anastomosis.</td>
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<tr>
<td>pH-dependent</td>
<td>The pH-dependent mesalamine preparations are coated with an acrylate resin and are released at variable pH levels between 6.0 and 7.0 in the distal ileum and colon. (The pH in the ileum and ascending colon is 7.0.)</td>
<td>Free 5-ASA (mesalamine) dosage can be maximized to 4.8 to 6 g daily, equivalent to a triple dose of sulfasalazine (12 g) with significantly less toxicity.</td>
<td>A pH-dependent delivery system is indicated in ileocolonic disease.</td>
</tr>
<tr>
<td>Colonic flora-dependent, azo-bonded</td>
<td>There are currently 3 variations of colonic-releasing, azo-bonded 5-ASA: olsalazine consists of 2 molecules of 5-ASA linked to each other; balsalazide links an inert polymer of 4-aminobenzoyl-L-alanine to 5-ASA; sulfasalazine consists of 5-ASA bonded to sulfapyridine.</td>
<td>In these azo-bonded 5-ASA forms, the molecule reaches the colon primarily intact, and the azo bond is cleaved by colonic bacterial azoreductase, thereby releasing free, unconjugated 5-ASA (mesalamine). A high-dose, 1.1-g balsalazide tablet allows for lower pill burden and twice-daily dosing.</td>
<td>Indicated for patients with universal and distal colitis.</td>
</tr>
<tr>
<td>Topical/rectal formulations</td>
<td>Rectal preparations include 5-ASA suspensions (4-g mesalamine enema and 500-mg mesalamine suppositories) instilled directly into the rectum.</td>
<td>Advantages of topical preparations include direct exposure to diseased mucosa.</td>
<td>Indicated for patients with left-sided colitis and proctitis.</td>
</tr>
</tbody>
</table>

5-ASA, 5-aminosalicylic acid; MMX, multimatrix
**TREATMENT OF UC**

Until the introduction of balsalazide, all of the newer 5-ASA agents had been shown to induce and maintain remission of UC nearly as well as sulfasalazine and usually as well as one another. The advantage of some of the newer 5-ASA preparations is that patients can tolerate higher doses (Figure 3). Recently, novel dual-delivery systems (delayed- and extended-release) allow for effective dose de-escalation, with lower doses of active 5-ASA delivered to the site of active colitis.$^{36-38}$

In the first head-to-head trial comparing an equimolar dose of balsalazide (6.75 g) with pH-dependent mesalamine (2.4 g), balsalazide showed superior efficacy in patients with new-onset left-sided UC (62% vs 37%) and shorter time to response (10 vs 25 days) compared with pH-dependent mesalamine. Response rates also were higher with balsalazide compared with pH-dependent mesalamine in patients with right-sided UC, although the difference was less significant compared with patients with left-sided disease.$^{39}$ A stratification study confirms that among patients with new-onset left-sided UC, more than 60% of those treated with balsalazide were in remission at 1 month compared with 40% of those treated with pH-dependent mesalamine. Additionally, patients with right-sided UC who were treated with balsalazide had less rectal bleeding, better sigmoidoscopic-evident healing, and improved stool frequency.$^{40}$ A new twice-daily balsalazide dosing regimen (3, 1.1-g tablets bid, for a total of 6.6 g/d) has been shown to be well tolerated and effective in relieving signs and symptoms of mild to moderate UC.$^{41,42}$ This new regimen reduces pill burden and should improve compliance and convenience for patients.

Levine et al conducted a randomized, double-blind study comparing 2 doses of balsalazide (6.75 and 2.25 g) and mesalamine (2.4 g) in patients with active, mild to moderate UC.$^{43}$ At week 8, rates of remission were similar for all 3 treatment groups, as were safety profiles. The primary difference between equimolar doses of balsalazide (6.75 g) and mesalamine (2.4 g) appeared to be the time to symptom resolution (10 vs 25 days). The more rapid onset of action of balsalazide may be related to greater 5-ASA delivery to the colon from the azo-bonded delivery system. The authors also observed that patients who received mesalamine 2.4 g had significantly higher steady-state plasma levels of 5-ASA and its N-acetylated metabolite at week 2 compared with patients who received balsalazide 6.75 g. This finding suggests the precolonic (ileal) absorption of 5-ASA from the pH-dependent delayed-release formulation of mesalamine. Further dose-ranging studies are required to establish the efficacy of high-dose mesalamine (4.8 g) and balsalazide (13.5 g). In a study that compared the colonic mucosal concentration of 5-ASA in patients treated with a mean of 6.75 g per day of balsalazide (free 5-ASA, 2.4 g/d) with those treated with a mean of 3.74 g per day of pH-dependent mesalamine (free 5-ASA, 1.6-6.0 g/d), patients who received balsalazide had significantly higher mean mucosal concentrations of 5-ASA than patients who received mesalamine.$^{44}$

Because of the predominance of left-sided disease, the combination of oral and topical aminosalicylates is critical in inducing and maintaining remission.$^{45,46}$ Safdi et al elegantly demonstrated that although topical mesalamine was more effective than oral in patients with left-sided UC, the combination of 2.4 g of oral mesalamine and mesalamine enemas produced earlier and more complete cessation of rectal bleeding.$^{45}$ For maintenance of remission, D’Albasio et al found that a combination of 1.6 g of oral mesalamine with twice-weekly mesalamine enemas produced higher rates of remission compared with oral therapy alone (61% vs 31%, respectively).$^{46}$ Topical mesalamine (enemas and suppositories), used as infrequently as twice per week,
is effective in maintaining remission in patients with distal colitis.

Biddle et al established that 75% of patients (9 of 12) randomized to receive mesalamine enemas remained in remission at 1 year compared with 85% of patients (11 of 13) on placebo who had relapsed by week 16.\textsuperscript{47} Similarly, mesalamine suppositories were associated with long-term remission in patients with ulcerative proctitis; at 12 and 24 months, 86% and 89% of patients on placebo had relapsed compared with 32% and 46% of patients treated with mesalamine suppositories, respectively. A meta-analysis established that in patients with left-sided UC and ulcerative proctitis, topical mesalamine showed greater efficacy and fewer side effects than oral therapies and topical steroids.\textsuperscript{49} Additionally, Campieri et al demonstrated that mesalamine suppositories were effective in inducing remission in patients with ulcerative proctitis (distal colitis up to 20 cm).\textsuperscript{50} In that study, 74% of patients who received mesalamine suppositories (1.5 g) achieved clinical remission at week 4 compared with 39% of patients who received placebo.

The pH-sensitive 5-ASAs were evaluated in a placebo-controlled trial in patients with mild to moderate UC.\textsuperscript{51} Complete remission was achieved in 24% of patients on mesalamine 4.8 g, 9% of patients on mesalamine 1.6 g, and 5% of patients on placebo. Partial response was noted in 50% of patients in the high-dose mesalamine group compared with 18% in the low-dose group and 13% in the placebo group. The ASCEND II trial found 4.8 g of delayed-release mesalamine (Asacol, Proctor & Gamble) to be superior to 2.4 g in patients with moderate UC, with response rates of 72% and 59%, respectively; remission rates were similar in both groups at 24%.\textsuperscript{52} ASCEND I and II were the first head-to-head—although non-placebo-controlled—comparisons of 2.4 versus 4.8 g of Asacol in patients with mild to moderate UC. In ASCEND III, the response rate at 6 weeks was 70% for patients taking 4.8 g of Asacol (6 tablets, 800 mg each) compared with 66% for those taking 2.4 g of Asacol (6 tablets, 400 mg each).\textsuperscript{53}

A high-strength formulation of 5-ASA—multimatrix (MMX) mesalamine (Lialda, Shire)—taken once or twice daily has been shown to be well tolerated and to induce remission in patients with mild and moderate UC. The formulation is a 1.2-g tablet and has been evaluated for twice-daily (1, 1.2-g tablet, bid; 2.4 g/d) and once-daily (4, 1.2-g tablets, once daily; 4.8 g/d) administration. Lichtenstein et al showed that after 8 weeks of treatment, rates of clinical and endoscopic remission were significantly higher for patients taking MMX mesalamine compared with patients taking placebo (34.1% and 29.2% for 2.4 g/d and 4.8 g/d, respectively, vs 12.9% for placebo; P<0.01).\textsuperscript{54,55} Increasing the dose to 4.8 g per day for an additional 8 weeks resulted in clinical and endoscopic remission and symptom resolution for nearly 60% of patients in a median time of 15 days.\textsuperscript{56} In a separate study by Kamm et al, once- or twice-daily MMX mesalamine resulted in maintenance of clinical and endoscopic remission.\textsuperscript{57}

In a recent dose-ranging study that evaluated a novel granulated formulation of 5-ASA in patients with mildly to moderately active UC, remission rates were 66% for patients taking 3 g per day (1 g, tid), 50% for those taking 1.5 g per day (0.5 g, tid), and 55% in those taking 4.5 g per day (1.5 g, tid).\textsuperscript{36} Although there was no placebo arm in the study, clinical remission rates in all 3 treatment groups were high. With the exception of endoscopic improvement, which was better in the 3-g per day group than in the 1.5-g per day group, no significant differences among the 3 groups were observed. These findings suggest that the novel delivery mechanism of granulated mesalamine may allow for effective dose de-escalation. In another study, 2 doses of mesalamine granules—a 3-g dose given once daily and a 1-g dose given 3 times per day—were similarly safe and effective in producing clinical and endoscopic remission in patients with mildly to moderately active UC.\textsuperscript{37} This provides evidence that decreasing the dosing frequency may improve adherence to medication while maintaining efficacy. Once-daily, 1.5-g granulated mesalamine delayed- (Eudragit-L, Degussa Rohm; dissolving at pH>6.0) and extended-release (polymer matrix core, containing slowly eluting mesalamine) have been shown to maintain remission in nearly 80% of patients who switched from different 5-ASA formulations compared with almost 60% who maintained remission on placebo.\textsuperscript{58} Dose de-escalation with granulated mesalamine 1.5 g per day may improve long-term adherence to medication and remission. Mesalamine granules also have demonstrated higher rates of induction of remission of UC compared with budesonide (54.9% vs 39.5%).\textsuperscript{59} And in a comparison of MMX mesalamine and Asacol, patients with UC who took MMX mesalamine maintained remission longer than those on Asacol.\textsuperscript{59}

**TREATMENT OF CD**

Compared with UC, the role of 5-ASA therapy in maintenance of remission of CD is not well defined.

The results of ACCENT I (A Crohn’s disease Clinical trial Evaluating infliximab in a New Long term Treatment regimen)—which established the efficacy of infliximab for maintenance therapy in CD—challenge the lack of effectiveness of maintenance strategies previously established by the multicenter National Cooperative Crohn’s Disease Study and European Cooperative Crohn’s Disease Study.\textsuperscript{60-62} These trials did not demonstrate a statistically significant benefit of sulfasalazine in the maintenance of remission of CD. Notably, only 20% to 30% of patients with CD have colonic disease alone, and most sulfasalazine is released in the colon. Subsequent smaller trials confirmed the lack of efficacy of sulfasalazine. All of these studies were flawed, in that they analyzed different disease sites (ileal, ileocolonic, colonic), different groups of patients (medical vs surgical), and different doses of medication.
With the introduction of mesalamine, higher doses of active 5-ASA have shown increased efficacy for both the induction and maintenance of remission in patients with CD.65 A meta-analysis of 10 randomized controlled trials evaluating mesalamine maintenance therapy in 1,371 patients with CD showed no statistically significant difference in relapse rates between treatment and placebo64; however, mesalamine treatment was associated with significantly lower relapse rates in patients with limited ileal disease of long duration.64

**COMBINING ORAL AGENTS**

Although there are no studies evaluating combinations of oral 5-ASA drugs, combination therapy can be considered in patients who fail to respond to mesalamine monotherapy or 5-ASA prodrug monotherapy. 5-ASA nonresponders may benefit from a combination of pH-dependent polymer-coated mesalamine, moisture-dependent mesalamine, and azo-bonded 5-ASA preparations (sulfasalazine, olsalazine, balsalazide). A flexible dosing schedule in which the patient actively modifies the combination therapy based on clinical response may shorten the duration to response. Lastly, a flexible dosing schedule that combines oral and topical 5-ASA agents is an effective therapeutic strategy that should not be overlooked. With the variety of 5-ASA preparations available, optimization of 5-ASA therapy may be viewed as a dynamic rather than a static process. In a patient not responding to an initial 5-ASA therapeutic choice, dosage may be optimized (escalated, de-escalated), and oral preparations may be combined with each other as well as with topical agents in an attempt to optimize delivery of 5-ASA to the site of active disease.

**Alternatives to 5-ASA: Management of 5-ASA Nonresponders**

Although 5-ASA compounds have been considered the cornerstone of induction therapy for both UC and CD, in selected cases, the earlier use of more potent medications—such as budesonide, AZA, 6-MP, MTX, anti-TNFs, and even surgery—may be considered. Approximately 30% of patients treated with 5-ASA agents are deemed nonresponders. These include patients who may be allergic, intolerant, nonadherent,65 underdosed, or refractory to treatment with 5-ASAs. Allergies or intolerance to 5-ASA agents may be diagnosed in patients who develop high-grade fevers or whose symptoms, upon careful evaluation, seem to worsen in response to 5-ASA treatment. In these patients, paradoxically, discontinuation of therapy improves their condition. Patients who respond to 5-ASA therapy may be distinguished from nonresponders on the basis of differences in clinical characteristics (eg, mucosal or transmural inflammation, fistulizing or strictureting CD), anatomic distribution (eg, proctitis, distal ulceration, or colitis in patients with UC: ileal, ileocolonic, colonic in patients with CD), or metabolic and signaling pathways.

**Ulcerative Colitis**

**Steroids** Steroids have been the mainstay of treatment for induction of remission in patients who do not respond to 5-ASA agents, and for patients with moderate to severe UC. Although steroids are effective in inducing remission, they are not effective in maintaining it. Furthermore, steroid dependence should not be confused with maintenance of remission. If possible, these agents should be avoided because they are associated with long-term AEs, including the development of avascular necrosis of the hip, osteoporosis, cataracts, glaucoma, diabetes, acne, and emotional disturbances.

Rectal steroid preparations are effective in treating distal disease, although they are less effective than rectal preparations of mesalamine.49,66 Furthermore, they have been associated with mild side effects. (Approximately 10% of a 100-mg dose of hydrocortisone in an enema is absorbed, ie, 10 mg of hydrocortisone is absorbed systemically).

**6-Mercaptopurine/Azathioprine** 6-MP and AZA have proven efficacious in the induction and maintenance of remission in patients with steroid-dependent UC. A long-term study by George et al showed that 65% of patients on long-term 6-MP therapy achieved maintenance of remission over a 5-year period.67

Adverse effects of 6-MP and AZA include bone marrow suppression with neutropenia (approximately 2%), pancreatitis (3%), hepatitis (0.3%), and infectious complications (7.4%), which may be attributed to concomitant steroid use.68 Pancreatitis is an idiosyncratic reaction and precludes any future therapy with 6-MP or AZA. Gastrointestinal (GI) intolerance with 6-MP may be avoided with AZA, and vice versa. Nausea with either agent can sometimes be avoided by taking the medication at bedtime.

6-MP and its prodrug AZA are metabolized by thiopurine methyltransferase (TPMT) to inactive 6-methylmercaptopurine (6-MMP; Figure 4). Normal or high levels of TPMT activity favor the production of the inactive metabolite 6-MMP, while an absence of TPMT or low levels of TPMT activity leads to the production of the active, and potentially toxic, metabolite 6-thioguanine (6-TG), which may result in bone marrow suppression. 5-ASA agents and furosemide also may inhibit TPMT activity. Increased production of the toxic metabolite can be minimized by reducing the dose of 6-MP/AZA.69 However, patients with normal or high TPMT activity should receive a full, weight-based dose of 6-MP (1.5 mg/kg) or AZA (2.5 mg/kg), shortening the time to response from more than 3 months to 1 month. A common error among clinicians is to underdose 6-MP or AZA.70 Measuring 6-TG levels in patients who are not responding to therapy is helpful and may identify patients who are nonadherent (low 6-TG levels), resistant to therapy, or at increased risk for bone marrow suppression (high 6-TG levels).71

One study reported a small absolute risk for non-Hodgkin’s lymphoma in patients with IBD, but only 5% of these cases were potentially associated with
immunomodulator therapy. Although an increased incidence of non-Hodgkin’s lymphoma was observed in patients with IBD on immunosuppressive therapy, the overall risk remains low.

Data support the safety of 6-MP therapy during pregnancy. One study concluded that when 6-MP is taken before and at conception, and also during pregnancy, it is not associated with an increased risk for premature birth, spontaneous abortion, congenital abnormalities, neonatal and childhood infections, or neoplasia. Further studies that evaluate the long-term toxicity of 6-MP and AZA are needed.

One study of IBD patients with long-standing, extensive UC who received thiopurine showed a 72% decrease in the incidence of colorectal neoplasia.

**Probiotics** A small study showed no significant benefit of probiotics in maintenance of steroid-induced remission of UC. Shanahan et al tested 2 probiotics—*Lactobacillus salivarius* and *B. infantis*—in patients with UC within 1 month of steroid-induced remission. In contrast to previous studies in animal models, neither probiotic showed a benefit compared with placebo. Notably, the probiotics were initiated after patients were on steroids, raising the question of how patients would have responded had the probiotics been initiated before steroid therapy.

**Cyclosporine** Cyclosporine should be reserved for patients with severe, medically refractory UC who either are not candidates for surgery or elect to avoid total proctocolectomy and ileal-anal anastomosis because of concerns about the 30% to 50% risk for postoperative pouchitis and decreased fertility. Treatment and management of pouchitis are addressed in the section on surgical treatment.

In 2 studies, more than 80% of patients with medically refractory UC responded to IV cyclosporine. One of the studies showed that nearly three-fourths of patients who initially responded to cyclosporine were able to avoid colectomy for a period of 5 years. Current data suggest that the chance of avoiding surgery after the induction of remission with cyclosporine is measurably improved when 6-MP or AZA is added early in the therapeutic regimen, underscoring the role of cyclosporine as a bridge to maintenance therapy with 6-MP or AZA. Because of concerns about nephrotoxicity, encephalopathy, and immunosuppression, cyclosporine is not a drug of choice for maintenance of remission.

**Biologics** Infliximab is approved for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy. The approval was based on 2 randomized, double-blind, placebo-controlled studies (ACT 1 and ACT 2 [Active Ulcerative Colitis Trials 1 and 2]) that evaluated the efficacy of infliximab for induction and maintenance therapy in adults with moderately to severely active UC. Researchers concluded that patients with moderately to severely active UC who were treated with infliximab at weeks 0, 2, and 6, and every 8 weeks thereafter, were more likely to have a clinical response at weeks 8, 30, and 54 than those who received placebo. A recent study showed that infliximab is effective in maintaining clinical remission and mucosal healing in patients with steroid-dependent UC, with one-third of patients requiring an increased dose. Response was better in patients with extensive colitis than in those with left-sided colitis.

Emerging data supporting early intervention with infliximab in patients with CD challenges clinicians to consider a similar early intervention strategy in patients with UC. Indeed, recent data confirm that late intervention with biologic therapy (either as monotherapy or combination therapy) in steroid-dependent, 6-MP/AZA-refractory UC patients is ineffective and does not diminish colectomy rates.

In a study of patients with infliximab-refractory UC, adalimumab was well tolerated, with long-term maintenance of response observed in 50% of patients. AEs requiring discontinuation of therapy occurred in less than 10% of patients. Additional recent data also support the use of adalimumab in patients with UC.

**Investigational Drugs** Golimumab (Simponi, Centocor Ortho Biotech), a novel anti-TNF, and vedolizumab (MLN-0002), a targeted α4β7 anti-integrin, have been investigated in the treatment of steroid-dependent patients with UC.

A small study has investigated the effect of rituximab in UC patients with antibodies to pANCA. Anti-B
lymphocyte therapy that decreases ANCA titers may be effective in ANCA-associated disease by eliminating antibody-producing cells and perhaps altering T regulatory cell function. Therefore, the concept of suppressing humoral antibody formation with use of anti-B lymphocyte neutralizing antibodies may be applied in the setting of UC. Rituximab, an anti-CD20 B cell antibody, has been effective in the treatment of rheumatoid arthritis. Further studies that evaluated its role in UC need to be conducted.

The investigational agent MDX-1100, which inhibits immune cell migration to gut epithelium, was found to relieve symptoms in patients with moderate to severe UC. However, the results were not statistically significant compared with treatment with a placebo, possibly a result of nonoptimal dosing of the agent. Further study with higher doses is warranted.

**Surgery for Medically Refractory UC** Despite aggressive optimization of medical therapies, UC remains a surgical disease. From 30% to 40% of patients with UC eventually require colectomy for indications of severe disease activity, chronic disease activity, dysplasia, or cancer.

Acute or chronic pouchitis may develop after colectomy in 15% to 50% of patients with UC. Acute pouchitis may respond to 1 or 2 cycles of either ciprofloxacin (250 mg bid) or metronidazole (250 mg qid) for 7 to 10 days. For chronic pouchitis, metronidazole is the treatment of choice. Patients with chronic pouchitis also may respond to therapy with probiotics. In a controlled study by Gionchetti et al, 100% of the patients with pouchitis treated with antibiotics relapsed compared with only 15% of patients treated with the probiotic VSL#3. All patients treated with VSL#3 relapsed within 3 months after discontinuation of the probiotic.

When chronic pouchitis becomes debilitating, 5-ASA agents, steroids, immunomodulators, and even infliximab may be required. Pouch excision and conversion to a Brooke ileostomy is required in rare cases. In selected cases, ileal pouch advancement should be considered as a surgical alternative to pouch excision.

A cost–utility analysis of infliximab compared with surgery for the treatment of patients with UC demonstrated that restorative proctocolectomy is less costly and more effective than treatment with infliximab, although the absolute difference in the increment cost and health benefit was minimal. Further research, including the development of valid utility measures for different states of UC, is needed.

**Crohn’s Disease**

When no other options exist, conventional steroids are appropriate and currently recommended by the American Gastroenterological Association for inducing remission in patients with moderate to severe CD who have not responded to 5-ASA therapy. Alternatives to therapy with conventional steroids now include treatment with budesonide, antibiotics, immunomodulators, anti-TNF agents, and novel biologic agents. Anti-TNF agents elicit a rapid response (within 2 weeks after administration) in up to 80% of patients. Although steroids also rapidly induce response in approximately 80% of patients, they have not altered the surgical rates in CD or the natural progression toward stricturing and fistulizing disease.

A comparison of early immunosuppression combined with infliximab versus early steroid therapy showed that “top-down” therapy with immunosuppression and infliximab allowed patients to remain steroid-free at the end of 2 years, and most importantly, was associated with mucosal healing rates of 73% compared with 30% in the “step-up” steroid therapy group. Maintenance of long-term remission may be possible in selected 5-ASA responders with mild disease, but many patients with moderate to severe disease require 6-MP, AZA, MTX, or anti-TNF agents. Currently, the evidence for the use of antibiotics for long-term maintenance therapy is anecdotal, and some reports looking at probiotics for maintenance of remission in CD are disappointing.

**Steroids** Almost 60% of patients with CD treated with steroids initially achieve remission. However, Munkholm et al showed that at the end of 1 year, 44% of patients had a prolonged response to steroids, 36% had become steroid-dependent, and 20% of patients were steroid-resistant.

A recent pharmacoeconomic study that evaluated the impact of continuous steroid use (>3 months) in patients with CD demonstrated significant costs for society and third-party payers. In steroid-dependent patients (>6 months of steroid use), short-term treatment with infliximab was ineffective as a bridge to maintenance therapy with AZA in both AZA-naïve and AZA-experienced patients.

The TREAT (Crohn’s Therapy, Resource, Evaluation, and Assessment Tool) registry provides evidence that patients on prolonged steroid therapy have an increased risk for serious infection. In this prospective patient registry designed to study the long-term safety of therapies for CD, the only medications independently associated with serious infections were prednisone (odds ratio [OR] 2.21; 95% confidence interval [CI] 1.46–3.33; P < 0.001) and narcotics (OR 2.11; 95% CI 1.10–4.05; P = 0.024). Despite having more severe CD, patients treated with infliximab had similar rates of mortality and malignancy, such as lymphoma, compared with patients not treated with infliximab. Six-year efficacy data from the TREAT registry revealed stable efficacy and safety data. Interestingly, despite emerging data that support early intervention with biologics and immunosuppressive agents and limited use of steroids, physician prescribing patterns have not significantly changed over the past 6 years.

**Oral Budesonide** Oral budesonide is a topically active, rapidly metabolized steroid that is released in the ileum and right side of the colon. Studies show that budesonide is superior to both placebo and mesalamine (4 g/d) for the induction of remission in patients.
with active Crohn’s ileocolitis, leading some experts to recommend budesonide as first-line therapy in mild to moderate Crohn’s ileocolitis.

An optimal response to budesonide (9 mg/d [3, 3-mg tablets every morning]) occurs within 10 days after administration. Although budesonide (3-6 mg) prolongs the time to relapse in patients with medically induced remission, it is not effective in maintaining remission at 1 year.11,14 Because budesonide is not effective for long-term maintenance, it may be used as first-line induction therapy for moderate Crohn’s ileocolitis and as a bridge to maintenance therapy with 6-MP or AZA. However, in patients with mild ileocolitis who are 5-ASA-naïve, the use of budesonide is debatable. The use of budesonide as a first-line therapy for mild ileocolitis may result in the overuse of immunomodulators for maintenance of remission. Budesonide (9 mg) and Eudragit-L-coated mesalamine (4.5 g) lead to high remission rates in patients with moderately active CD.115 However, granulated mesalamine was associated with a shorter time to remission compared with budesonide.

**Antibiotics** The rationale for using antibiotics in CD is related to the concept that environmental triggers that alter indigenous luminal bacteria (eg, traveler’s diarrhea, gastroenteritis) or mucosal barrier function (eg, acute infections, nonsteroidal anti-inflammatory drugs) increase mucosal inflammation and permeability.117 A study implicating IBD and pouchitis as a reactive enteropathy to Group D Streptococcus (Enterococcus) underscores the importance of luminal bacteria in exaggerated immune response.117 Metronidazole is effective for the induction and maintenance of remission in CD patients with perianal disease, and also for the prevention of postoperative endoscopic and clinical recurrences (when given for 3 months following ileal resection).118-120 The combination of ciprofloxacin (500 mg bid) and metronidazole (250 mg qid) has been shown to be almost as effective as methylprednisolone in the treatment of patients with active CD.121 Rifaximin, an orally administered, topically active nonabsorbable antibiotic with proven efficacy in traveler’s diarrhea,122 also may be effective for induction and/or maintenance of remission of CD.123

**6-MP/AZA** Among patients with active CD, 67% of those treated with low-dose 6-MP (50 mg) showed overall clinical improvement compared with 8% of patients on placebo.124 Additionally, treatment with 6-MP resulted in complete closure of 31% of fistulas versus 6% of fistulas in the placebo group. However, time to response was more than 3 months in 50% of patients.

In a 15-month, double-blind controlled maintenance study of AZA, 42% of patients who received AZA 2.5 mg/kg maintained remission compared with 7% of patients who received placebo.125

In children with CD, early introduction of 6-MP therapy allowed maintenance of steroid-free remission126; only 9% of children relapsed during therapy with 6-MP compared with 47% of patients in the control group. Further studies that investigate the use of 6-MP before the initiation of steroids are warranted.

Assessment of TPMT activity and identification of patients with suboptimal levels of the active metabolite 6-TG (indicating 6-MP resistance) are warranted in patients with CD, as for patients with UC (Figure 4). Patients with high TPMT activity and preferential production of the inactive metabolite 6-MMP, low-dose allopurinol (a xanthine oxidase inhibitor) may be effective in shunting metabolism toward 6-TG.128

An increased risk for lymphoproliferative disease and infection with Epstein-Barr virus has been associated with AZA therapy.129

**MTX** One study of patients with active CD showed that with 4 months of therapy with MTX (25 mg intramuscularly, weekly), 39% of patients achieved clinical remission compared with 19% of patients in the placebo group.130 In a follow-up study evaluating MTX for maintenance of remission, 65% of patients on MTX (15 mg intramuscularly, weekly) maintained remission compared with 39% of patients on placebo.131

In steroid-dependent patients with a forced steroid taper over 14 weeks, there was no difference between treatment with MTX in combination with infliximab and monotherapy with infliximab, suggesting that there is no need for immunosuppression with regularly scheduled infliximab monotherapy.132 A recent study evaluated the effect of MTX on the formation of antibodies to infliximab and infliximab trough concentrations.133 In this study, the combination of infliximab and MTX, although safe, was no more effective than infliximab alone in CD patients who required treatment with prednisone. However, patients treated with MTX were less likely to form antibodies to infliximab and more likely to have high serum trough levels of infliximab. Notably, detectable infliximab trough levels were associated with treatment success, independent of treatment with MTX.

**Tacrolimus and Cyclosporine** Tacrolimus and cyclosporine continue to have a role in the treatment of patients with CD. Tacrolimus (0.10 mg/kg bid) has been shown to close perianal fistulas in patients with medically and surgically refractory CD.134,135 In a study of cyclosporine, 59% of steroid-dependent or steroid-intolerant patients responded to cyclosporine (7.5 mg/kg per day) over a period of 3 months compared with 32% of patients in the placebo group.136

**Infliximab** Infliximab is highly effective for the treatment of moderately to severely active, medically refractory, inflammatory, and fistulizing CD.137 Four weeks after a single infusion of infliximab 5 mg/kg, 81% of patients showed a clinical response compared with 17% of patients in the placebo group.98

The role of infliximab in maintenance therapy continues to be defined. In the ACCENT 1 trial, a large, multicenter, controlled study of infliximab maintenance therapy, 39% and 45% of patients on infliximab (5 and 10 mg/kg, respectively) achieved clinical remission at week 30 compared with 21% of patients on placebo.60 In another controlled trial of infliximab (5 mg/kg, given in 3 doses) maintenance therapy, infliximab was associated
with complete closure of fistulas for a median 3 months in 46% of patients, and a 50% reduction in fistula drainage in 62% of patients. A recent study evaluated long-term scheduled infliximab therapy in patients with CD. Approximately 75% of those who discontinued therapy experienced a flare, arguing that infliximab maintenance was still necessary.

In May 2006, infliximab was approved for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy. The REACH study evaluated the safety and efficacy of infliximab in children with moderately to severely active CD. At week 54 of treatment, more than half of patients who received infliximab every 8 weeks had achieved a clinical response and were in clinical remission, respectively, and did not require dose adjustment. At the end of 1 year, almost 50% of children who received infliximab every 8 weeks were in remission and no longer on steroids, compared with 17% of children who received infliximab every 12 weeks. In a follow-up study after stable remission—achieved with infliximab and immunosuppression for at least 1 year—more than half of patients did not relapse after discontinuation. For those who did relapse, infliximab retreatment was well tolerated and induced remission.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported with both infliximab and adalimumab; all of the cases occurred in patients on concomitant treatment with AZA or 6-MP. Updated data from the TREAT registry revealed no increased risk for lymphoma with infliximab. However, a recent analysis of IBD patients treated at a tertiary academic medical center did find an increased risk for lymphoma; this risk was associated with older age, however, the authors also acknowledged a potential association with severe disease or IBD medications (eg, 6-MP, AZA, infliximab).

A recent prospective randomized switch study examined CD patients in clinical remission on infliximab maintenance therapy, approximately half of whom were switched to adalimumab therapy. Significantly more patients crossed over from the adalimumab group to infliximab therapy than vice versa (8 vs 0; P=0.002). Although a majority of patients on adalimumab preferred it to infliximab, the study showed that an elective switch to adalimumab is not recommended for patients who are in stable remission on infliximab. However, a switch from adalimumab to infliximab may be beneficial in patients who are intolerant or exhibit an attenuated response to adalimumab. Optimization strategies for all of the anti-TNF agents need to be defined.

SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) is the first large, prospective, head-to-head trial that supports a tectonic shift toward early intervention with anti-TNF therapy and away from unlimited steroid use in patients with active moderate to severe CD.

**Immunomonitoring for Infliximab** Immunogenicity to infliximab, which may reduce the efficacy of treatment and/or induce AEs, has been recognized in some patients treated with infliximab. Monitoring of infliximab trough level and antibodies to infliximab—and, arguably, TNF levels—may allow for optimization of therapy. A recent study by Van Moerkercke et al showed that CD patients with complete mucosal healing on infliximab treatment had significantly higher infliximab trough levels than patients who did not achieve complete healing.

Currently, the detection of antibodies to infliximab depends on a solid-phase assay that is limited by circulating infliximab masking the presence of antibodies to infliximab; therefore, accurate antibody levels generally are detected at 8 weeks after infliximab infusion, allowing for clearance of infliximab from the serum. Recently, a novel, highly sensitive liquid-phase assay that measures infliximab levels and antibodies to infliximab has been evaluated, and may allow for more frequent immunomonitoring.

**Adalimumab** Adalimumab was approved in 2007 for inducing and maintaining clinical remission in adult patients with moderate to severe CD who have had an inadequate response to conventional therapy and for inducing remission in these patients if they also have lost response or are intolerant to infliximab.

Adalimumab, a fully humanized anti-TNF antibody, was demonstrated to be superior to placebo for the induction of remission in patients with moderate to severe CD who were naïve to anti-TNF therapy and to maintain clinical remission for up to 56 weeks in these patients. Furthermore, among patients who were intolerant or did not respond to infliximab therapy, adalimumab induced remission more frequently than placebo.

In CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance), Colombel et al reported that among patients who initially responded to adalimumab, there were significantly higher rates of remission in patients on adalimumab versus those on placebo at 1 year. A subanalysis of CHARM revealed that in patients with CD for less than 2 years, approximately 50% of patients who received adalimumab (40 mg, subcutaneously, every week or every other week) maintained remission for more than 1 year. In an open-label extension of this trial, 28% of patients on adalimumab were in steroid-free remission at 3 years.

A recent "real-world clinical practice” dosage pattern study showed that patients who received adalimumab 160/80 mg as induction therapy were less likely to require weekly dosing compared with patients who did not. In the ACCESS trial, adalimumab was associated with clinically meaningful remission in both infliximab-exposed and infliximab-naïve patients. In a 6-month open-label analysis of the ACCESS trial, adalimumab was effective in inducing and maintaining steroid-free remission and fistula closure in both anti-TNF-naïve and anti-TNF–experienced patients. Adalimumab also was shown to be associated with the induction and maintenance of fistula healing both...
in anti-TNF– naïve and anti-TNF–exposed patients.\textsuperscript{152}

\textbf{Mucosal Healing With Adalimumab} The EXTEND (Efficacy of Adalimumab Through Endoscopic Healing) trial was a randomized, placebo-controlled study of mucosal healing in patients with moderate to severe ileocolonic CD who received adalimumab 160/80 mg on induction and were then randomized to receive adalimumab 40 mg every other week or placebo.\textsuperscript{153} Endoscopic evaluation was performed at weeks 12 and 52. The presence of mucosal healing at week 12 predicted 1-year outcomes, including Crohn’s Disease Activity Index score and clinical remission, with statistical significance for patients in the adalimumab treatment group.

The EXTEND study also revealed an association between increased rates of mucosal healing and early CD of less than 5 years’ duration in patients treated with adalimumab, suggesting that earlier intervention may favorably impact the natural history and progression of CD.\textsuperscript{154} Additionally, long-term data showed that remission of CD was maintained in a high percentage of patients whose dosing frequency was reduced from weekly to every other week.\textsuperscript{155}

\textbf{Immunomonitoring for Adalimumab} Low trough levels of adalimumab are associated with discontinuation, suggesting a role for immunomonitoring of adalimumab trough levels.\textsuperscript{156} However, a recent study showed that serum concentrations of adalimumab did not consistently correlate with clinical remission through 56 weeks of maintenance therapy.\textsuperscript{157}

\textbf{Certolizumab} Certolizumab pegol is a pegylated Fab’ fragment of a humanized monoclonal antibody (mAb) that neutralizes TNF-\(\alpha\). The FDA approved the drug in April 2008 for treatment of patients with CD who have had an inadequate response to conventional therapy. A Phase III, randomized double-blind, multicenter study that assessed the efficacy and tolerability of certolizumab in patients with moderate to severe CD showed a modest improvement in response rates compared with placebo, but no significant improvement in remission rates.\textsuperscript{28} Patients who initially responded to induction therapy with certolizumab were more likely to maintain response and remission at 26 weeks with continued treatment compared with a switch to placebo.\textsuperscript{29}

Results from the induction phase of the PRECiSE 2 (PEGylated Antibody Fragment Evaluation in Crohn’s Disease Safety and Efficacy) trial compared favorably with other monoclonal anti-TNF induction studies. The 6-week response rate of approximately 66% and remission rate of approximately 40% were unaffected by concomitant use of immunosuppressants or corticosteroids.\textsuperscript{158} Long-term 52- and 54-week data of certolizumab (400-mg, subcutaneous injection, given monthly) suggest that certolizumab is well tolerated.\textsuperscript{159} in more than 900 patients treated with certolizumab for 1 year, the incidence of infections and malignancy was similar to rates with other anti-TNF agents.\textsuperscript{159}

Preliminary results of the WELCOME (26-Week open-label trial Evaluating the clinical benefit and tolerability of certoliZumab pegol induCtiOn and Maintenance in patients suffering from CD with prior loss of response or intolErance to infliximab) trial showed that nearly 66% of patients who had lost response or were intolerant to infliximab responded to induction with certolizumab at weeks 0, 2, and 4, with maintenance every 2 or 4 weeks.\textsuperscript{160} Additionally, almost 40% of those patients achieved remission on certolizumab.\textsuperscript{160}

More than two-thirds of patients with CD duration of less than 1 year maintained remission with certolizumab at 26 weeks compared with 44% of patients with CD duration more than 5 years.\textsuperscript{28,161} Low levels of C-reactive protein (CRP) correlate with higher rates of maintenance healing with certolizumab.\textsuperscript{162}

Sandborn et al reported in the WELCOME trial that 62% of patients with moderate to severe CD who had previously responded to infliximab and lost response or who developed hypersensitivity to infliximab responded to open-label induction therapy with certolizumab.\textsuperscript{163} Among those who responded to certolizumab, 400 mg every 4 weeks was as effective as 400 mg every 2 weeks for maintenance of response and remission of CD over 26 weeks. In another analysis of the WELCOME study, Feagan and colleagues found that certolizumab improved health-related quality of life in patients with CD who had failed previous treatment with infliximab.\textsuperscript{164} Another analysis of the WELCOME study revealed that certolizumab induced a clinical response in patients with moderate to severe CD who had failed treatment with infliximab, regardless of the dose of infliximab used.\textsuperscript{165} An analysis of certolizumab use during pregnancy revealed, unlike infliximab, the presence of low levels of certolizumab in the cord blood of pregnant patients on the drug.\textsuperscript{166}

A recent observed case analysis study by Sandborn et al examined the long-term outcomes of patients with or without previous exposure to anti-TNF medications who were enrolled in the PRECiSE 4 certolizumab reinduction trial.\textsuperscript{167} At years 1, 2, 3, and 4, remission rates were 63%, 70%, 63%, and 58%, respectively, for patients who had received active treatment or placebo in the PRECiSE 2 trial; rates in the infliximab-naïve cohort were 68%, 71%, 60%, and 63%, respectively. This study demonstrated that certolizumab was associated with long-term remission, regardless of prior anti-TNF exposure. Notably, only one reinduction dose was evaluated in the PRECiSE 4 trial, the dosage was not weight-based, and no immunomonitoring of certolizumab levels in tissue or serum was reported.

\textbf{Combination Therapy: Anti-TNFs and Immunosuppression} Emerging data support the role of early intervention with biologic therapy in patients with CD. In an administrative claims database study of patients with CD, patients treated with a step-up course of therapy were more likely to require dose escalation of biologics or discontinuation and/or switch of biologic treatment and surgery compared with patients who were treated with biologics early in the course of disease.\textsuperscript{168} SONIC is a large, definitive, randomized, double-blind controlled trial that compared infliximab monotherapy,
AZA monotherapy, and a combination of infliximab and AZA therapy in patients with moderate to severe CD of short duration. Patients in the trial had been exposed to steroids but were naive to biologics or immunomodulators. Data revealed that for patients with evidence of inflammation (defined by CRP levels and endoscopic lesions), superior steroid-free clinical remission was associated with early infliximab combination therapy or infliximab monotherapy compared with AZA alone. Safety outcomes were similar in all 3 arms of the study. SONIC is a landmark study supporting the tectonic shift toward early intervention with anti-TNF therapy and away from unlimited use of steroids and AZA.

Data from the SONIC trial emphasize the importance of establishing evidence of inflammation before early intervention with biologics. Changing treatment based on clinical symptoms alone may lead to inappropriate management. CRP is a good noninvasive marker to use to monitor patients with CD who are being treated with infliximab; it may predict a loss of response and the need for adjustments in medications. A recent study showed that patients with antibodies to infliximab did not respond to higher doses of infliximab, whereas patients who exhibited nontherapeutic levels of infliximab responded to dose escalation and to a different anti-TNF agent. Assessment of antibodies to infliximab may be useful in determining therapeutic strategy. For example, if a patient has therapeutic levels of infliximab and is clinically symptomatic, the physician should perform an endoscopy to assess whether there is actual endoscopic evidence of inflammation. If there are no endoscopic lesions, consider other reasons for intractability, such as pseudorefractory CD.

Moving treatment from symptom-oriented strategies toward risk assessment and prevention-oriented strategies is predicated on establishing evidence of inflammation (eg, elevated levels of CRP, fecal calprotectin, emerging biomarkers) and mucosal healing, and underscores the importance of making an accurate diagnosis. In the absence of inflammation, “refractory” CD may in fact be pseudorefractory, due to bile acid diarrhea, celiac disease, lactose intolerance, irritable bowel syndrome, bacterial overgrowth, adhesions, or intestinal infections (eg, Salmonella, Shigella, Giardia, C. difficile). Intestinal obstruction, due to stricture, lymphoma, or carcinoma, also may be the cause of symptoms in patients without evidence of mucosal inflammation. Evidence of mucosal inflammation, elevated sedimentation rate, and elevated CRP levels should be documented before consideration of anti-TNF therapy. Mucosal healing in CD is strongly associated with decreased rates of hospitalization and intestinal resection. In contrast, symptomatic improvement is weakly correlated with mucosal healing. Endoscopic lesions may be helpful in identifying selected patients who are more likely to respond to early anti-TNF immunotherapy or combination therapy. Normal levels of CRP and mucosal healing are helpful in monitoring response and predicting success of discontinuation of infliximab.

In a small study, 17% of patients with normal CRP levels and no evidence of endoscopic lesions responded well when infliximab was withdrawn. Further anti-TNF withdrawal and dose de-escalation trials are warranted. Natalizumab Approved by the FDA in January 2008, natalizumab is a humanized IgG4 mAb against α4 integrin that also is used to treat multiple sclerosis (MS). Natalizumab has shown some improvement in response and remission rates in patients with CD; however, the drug has been associated with 3 cases of progressive multifocal leukoencephalopathy (PML) in clinical trials. The cases occurred in 2 patients with MS who were receiving combination therapy with natalizumab and interferon β-1a, and 1 patient with CD who was treated with natalizumab and had prior exposure to AZA and steroids and an underlying lymphopenia. Subsequently, no new cases of PML were identified in patients with CD who were treated with natalizumab in clinical trials. A recent report suggested a risk for PML of roughly 1 in 1,000 for patients treated with natalizumab for a mean of 17.9 months. Currently, more than 45,000 patients—mostly patients with MS—have been treated with natalizumab, with rare new cases of PML reported (13 cases, all in patients with MS). There also have been some reports of liver abnormalities. Because PML was associated with combination therapy in patients taking natalizumab, the FDA has approved this therapy as monotherapy in patients with CD.

A randomized, placebo-controlled trial of natalizumab induction therapy in patients with CD reported response and remission at week 8 that persisted through week 12; response and remission rates at weeks 4, 8, and 12 of the study were superior compared with patients taking placebo; demonstrating early and sustained efficacy of natalizumab as induction therapy. Natalizumab was well tolerated in this study.

Post hoc subgroup analyses of the ENACT (Efficacy of Natalizumab as Active Crohn's Therapy) 2 and ENCORE (International Efficacy of Natalizumab in Crohn's Disease Response and Remission) maintenance trials of natalizumab found consistently higher induction of remission rates for nearly 25% of patients with short-duration CD (<3 years). In the ENCORE trial, approximately 38% of patients who failed treatment with infliximab achieved a sustained response at weeks 8 and 12 on natalizumab compared with 17% of those on placebo. Remission rates at week 12 were unaffected by concomitant use of immunosuppressants in nearly 40% of patients. Two-thirds of patients in the ENCORE trial were not taking immunosuppressants.

A new validated assay provides a preliminary classification of patients may be at risk for the development of PML. PML has been shown to develop in patients who had prior infection with JC virus, as measured by the presence of antibodies. The new assay uses anti-JC antibodies as a means of stratification of risk for PML.

Novel Biologics for CD Teduglutide is a non–TNF-α biologic. The compound is an analog of the naturally occurring human peptide glucagon-like peptide-2, a growth
factor secreted in the distal intestine that is involved in regeneration, maintenance, and repair of the intestine. In an exploratory study designed to elicit proof of concept in CD, veduglutide was safe and effective for induction of remission in patients with moderate to severe CD as early as week 2, with an increase in remission rates at week 8.\(^{189}\) AEs were generally self-limited and mild.

Vedolizumab (MLN-0002) is a mAb targeting integrin \(\alpha_4\beta_7\) that selectively inhibits lymphocyte recruitment in the GI tract. One study showed that vedolizumab 2 mg/kg induced a significantly higher rate of clinical remission in patients with CD compared with placebo.\(^{90}\) A recent study showed that vedolizumab has not been associated with PML or any opportunistic infections to date.\(^{190}\) No association was found between treatment with vedolizumab and JC viremia, indicating that vedolizumab may be associated with a lower risk for PML.

Ustekinumab is a mAb against the P40 subunit of IL-12/23. This biologic induced a clinical response in patients with moderate to severe CD, especially patients who either never exhibited a response to infliximab or those who exhibited an attenuated response.\(^{91}\)

PF-00547,659 is a fully human anti-mucosal adhesion molecule (MAdCAM) IgG2 antibody that has shown favorable efficacy against adhesion molecules to MAdCAM in patients with moderate UC.\(^{192}\)

The oral \(\alpha_4\)-integrin inhibitor AJM300 has shown efficacy in patients with CD at 120 and 240 mg.\(^{93}\)

Abatacept is a biologic that binds to the \(\beta_1\) protein on the antigen-presenting cell to prevent the costimulatory signal required for T-cell activation. In a study of this biologic in patients with moderately to severely active CD who were refractory or intolerant to other medical therapy, abatacept was not effective for induction of response and remission.\(^{194}\)

Traficet-EN (CCX282-B), an oral CCR9-specific chemokine receptor antagonist that prevents immune cell recruitment to the intestine, has shown encouraging results in a 12-week induction and maintenance trial.\(^{195}\) At 36 weeks, 47% of patients on Traficet-EN were in remission compared with 31% of patients on placebo. Additionally, 41% of patients on Traficet-EN were in steroid-free remission versus 28% of patients on placebo.

**Surgery for Medically Refractory UC** Like UC, CD remains a surgical disease, with 70% to 80% of patients requiring surgery. Laparoscopic ileocolic resection has shortened recovery time and hospital length of stay for patients with medically refractory CD.\(^{196,197}\) With the availability of minimally invasive laparoscopic techniques and novel bowel-sparing stricturoplasty, earlier surgical intervention may be advantageous.\(^{198,199}\)

In patients with perianal disease, a combination of infliximab and surgery was associated with closure of perianal fistulas and a reduction in the rate of recurrent abscesses.\(^{200}\)

A recent study of patients on long-term anti-TNF therapy suggested that earlier intervention with primary anti-TNF therapy may decrease secondary attenuation of response and resection rates.\(^{201}\) Despite the efficacy of anti-TNF therapy, nearly two-thirds of patients required either reinjection or therapeutic switch within the class, and surgery was necessary in nearly one-third of patients.

Another recent study revealed no decrease in surgery rates over the past 10 years in a case series of patients treated episodically with infliximab.\(^{202}\) In this study, biologic therapy was introduced late in the course of disease in 6-MP/AZA-refractory patients. There was no characterization of dose or duration of steroid therapy in this study. Again, this underscores that prolonging the administration of biologics delays, but does not prevent, surgery.

The annual incidence of clinically significant postoperative recurrence of disease is 8% to 10%; strictureing disease tends to develop more slowly, and fistulizing disease tends to recur faster.\(^{203}\) The severity of clinical postoperative recurrences can be predicted by the severity of endoscopic anastomotic lesions. According to a study by Rutgeerts et al, endoscopically recurrent lesions developed in 73% of patients within the first year after ileocolonic resection.\(^{18}\) Three years after surgery, the endoscopic recurrence rate increased to 85%, and symptomatic recurrence was noted in 34% of patients. Those in whom diffuse, deep new ileal recurrences developed within 1 year tended to experience early symptoms and complications.\(^{18}\)

Studies show a decreased risk for postoperative recurrence of CD associated with treatment with 5-ASA,\(^{204,205}\) 6-MP/AZA,\(^ {206,207}\) VSL#3,\(^ {208}\) and infliximab.\(^ {209}\) In one study, postoperative infliximab therapy significantly lowered risk for endoscopic recurrence at 1 year in patients with complex fistulizing CD.\(^ {209}\) Only 9% of patients who had undergone an ileocolonic resection had a documented endoscopic recurrence after 1 year of postoperative infliximab (3-dose induction, followed by treatment every 8 weeks for 1 year). The rate of AEs was similar in the infliximab group and the placebo group (the placebo group included patients on AZA and 6-MP). Additional prospective studies are needed to establish the duration of postoperative maintenance of remission and to define the appropriate interval of postoperative endoscopic evaluations.

In a 2-year postoperative follow-up of patients treated with infliximab after surgery, infliximab was associated with maintenance of remission, but not after infusions were stopped.\(^ {210}\) A recent 4.5-year follow-up study of patients treated with infliximab after surgery showed maintenance of remission with ongoing infliximab infusions, but disease recurred if infliximab was discontinued.\(^ {211}\) Anti-TNF–naïve patients who develop postoperative endoscopic recurrence of CD at 1 year may be effectively treated with infliximab. A retrospective study found that early-phase administration of infliximab might contribute to the prevention of progression of mucosal damage.\(^ {212}\)
Conclusion

Identification of selected patients with moderate to severe IBD who will benefit from early therapeutic intervention—with immunomodulators and/or biologics—may result in decreased use of steroids and may slow or reverse progression of immune-mediated inflammation in the gut. The recent expansion of indications for anti-TNF and anti-integrin therapies and the demonstrated success of early intervention with a top–down approach (ie, the use of infliximab and immunosuppressants in steroid-naïve patients)\(^9\) suggest that earlier use of immunomodulators and/or biologic agents in patients early in the course of disease (<2 years) may prove to be steroid-sparing and may reduce the risk for colectomy in patients with UC and stricturing and fistulizing structural damage in patients with CD. The use of immunosuppressants and/or biologic agents as induction and maintenance therapy in steroid-naïve patients (or after short-term use of steroids) may be associated with fewer AEs\(^8,209\) compared with the use of these agents in patients on long-term steroid therapy.\(^108,213\) The administration of immunosuppressants and biologics to patients on long-term steroid therapy puts a small group of patients at risk for IBD-associated immune deficiency. Clear guidelines for the prevention of opportunistic infections and registries that document the risk for lymphoma and cancer in patients with moderate to severe IBD need to be established.\(^214\)

In selected patients with moderate to severe IBD, an earlier aggressive treatment approach is indicated. Some patients with mild to moderate disease may benefit from a decrease in medication dosage, adherence to therapeutic regimens, and in some cases, a reevaluation of the diagnosis. Identification of immunologically vulnerable patients through the use of emerging serologic markers, biomarkers, and genotyping may allow for individualized treatment that improves outcomes.

A greater understanding of the human genome is redefining the science of individuality. Less than 0.1\% of our DNA is responsible for IBD susceptibility and therapeutic response.\(^215-218\) We are at the threshold for genotyping patients and bacteria, which will lead to a greater understanding of the pathobiology of IBD and its treatment.\(^219\)

Until genomics can be applied to individualized medicine, predicting IBD progression may be achieved through risk assessment (eg, postoperative endoscopic evaluation, emerging biomarkers) and refining therapeutic strategies (eg, earlier, aggressive intervention in patients with severe disease; dose escalation in patients with less severe disease).

In selected patients with moderate to severe IBD, early intervention with immunosuppressive or biologic therapies—and limited use of steroids—may slow the progression of IBD and shift the treatment paradigm from a symptom-oriented, step-up strategy to a prevention-oriented, early intervention approach.

References


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