Crohn’s and Colitis: Treatment of 5-ASA Responders and Nonresponders

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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 risk assessment, rather than treating symptoms.

The greatest challenge for clinicians today 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 treating IBD is whether the disease is a single entity or a spectrum of multiple disorders. This distinction becomes particularly difficult 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 nonpseudoloeid 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,
Molecular Classification of IBD

IBD nomenclature does not accurately reflect the complexity of clinical phenotypic behavior. Although the role of serum antibody markers remains controversial, combining markers enhances their 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. Although new genes (identified by genome-wide association scans; regulating the interleukin (IL)-23 pathway, autophagy controls intracellular bacteria, and NOD2 protein regulating innate immune response through bacteria sensing) continue to highlight host microbial interactions, serologic markers observe deregulated 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. 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 proved helpful in patient stratification. Although there is controversy, high levels of perinuclear antineutrophil cytoplasmic antibodies (pANCA) have consistently correlated with postoperative pouchitis. Anti-CBir1 is an antibody to flagellin of the *Clostridium* species and increases the incidence of chronic pouchitis in patients who have high pANCA levels and predicts acute pouchitis when associated with low pANCA levels. Anti-*Saccharomyces cerevisiae* antibody positivity (expression of both immunoglobulin [Ig] subtypes A and G) correlates with a younger age at onset and more aggressive fibrotic disease. In addition, antibodies against the CD-related bacterial sequence I2, *Escherichia coli* outer membrane porin C, and CBir1 flagellin identify a unique subset of immunologically vulnerable patients with complicated/aggressive CD.

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 allow for risk assessment and advance prevention-oriented therapies and the science of IBD.

Treatment of IBD Subtypes

The goals of IBD treatments are universal: induce remission as quickly as possible, maintain remission as long as possible, facilitate mucosal healing, improve the patient’s quality of life, avoid toxicity, and minimize cost.

For patients with UC, oral and rectal 5-ASA (including free 5-ASA and 5-ASA prodrugs), corticosteroids given either intravenously (hydrocortisone) or orally (prednisone, methylprednisolone), immunomodulators (eg, azathioprine [AZA] and 6-mercaptopurine [6-MP]), and cyclosporine are used to induce remission. For maintenance of remission of UC, 5-ASA and 6-MP or AZA may be used. In addition, 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.

For patients with CD, 5-ASA, antibiotics (metronidazole, ciprofloxacin, alone or in combination),

Figure 1. Disease distribution of ulcerative colitis at presentation to the physician’s office.
corticosteroids (including topically active, rapidly metabolized budesonide), immunomodulators (6-MP, AZA, methotrexate), and infliximab are used to induce remission. For maintenance of remission, 5-ASA, antibiotics, immunomodulators, and infliximab can be used. Most recently, the anti-TNF agents adalimumab and certolizumab have been approved 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 to or are intolerant to infliximab.18-23

Probiotics and novel antibiotics (rifaximin) have the potential to revolutionize the approach to IBD.24 However, a greater understanding of the gut microecology and further clinical trials studying these agents are needed.

5-ASA: First-Line Therapy

**Mechanisms of Action**

The specific goals of 5-ASA therapy are to quickly induce a 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 and 5-lipoxygenase pathways of arachidonic acid metabolism, resulting in a decrease of proinflammatory prostaglandins and leukotrienes.25 Although clinical trials with leukotriene inhibitors and IL-10 have been disappointing, the role of the cyclooxygenase pathway and prostaglandin biosynthesis in IBD remains to be elucidated. Attention has shifted from the arachidonic acid cascade to nuclear factor-κB (NF-κB). The discovery of the role of NOD2 in the activation of NF-κB emphasizes the importance of NF-κB in the inflammatory signaling cascade and interaction with luminal bacterial antigens and genetic susceptibility.

Studies in cell cultures demonstrate that sulfasalazine inhibits NF-κB, supporting the direct biologic efficacy of 5-ASA. The question clinicians should ask is: Does the site of 5-ASA release matter in terms of optimizing and individualizing therapy? The 2 therapeutic strategies expose opposing views. One view is that all 5-ASA preparations are the same and equivalent: Both mesalamine (free, unconjugated 5-ASA) and prodrugs (azo-bonded 5-ASA) have similar modes of action. The other view is that subtle differences in 5-ASA delivery translate into clinical efficacy, allowing for optimizing strategies. Often overlooked is the distribution of UC; more than 50% of patients have left-sided disease (Figure 1).26

Sulfasalazine, the archetypal azo-bonded 5-ASA-containing 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.27

**Treatment of UC**

Until the introduction of balsalazide, all of the newer 5-ASA agents had been shown to induce and maintain remission in patients with UC nearly as well as sulfasalazine and, mole for mole, usually as well as one another. The advantage of the newer preparations is that patients can tolerate higher doses of the agents (Figure 3). The
### Table. Mechanisms of Release of 5-ASA-Containing Drugs

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Advantage</th>
<th>Indication</th>
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<tbody>
<tr>
<td><strong>Diffusion-dependent</strong></td>
<td>Time-released, moisture-dependent ethylcellulose-encapsulated mesalamine that travels in solution; 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>
</tr>
<tr>
<td><strong>pH-dependent</strong></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 6.0 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><strong>Colonic flora-dependent, azo-bonded</strong></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).</td>
<td>Indicated for patients with universal and distal colitis.</td>
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<tr>
<td><strong>Topical/rectal formulations</strong></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>
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- **Diffusion-dependent:**
  - mesalamine controlled release, Pentasa, Shire
  - Time-released, moisture-dependent ethylcellulose-encapsulated mesalamine that travels in solution; 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.
  - Independent of pH or bacteria; mucosal delivery of mesalamine is less affected by rapid intestinal transit time (ie, diarrhea).
  - 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.

- **pH-dependent:**
  - mesalamine delayed release (pH 7.0), Asacol, Procter & Gamble
  - multimatrix (MMX) mesalamine (pH 7.0), Lialda, Shire
  - mesalamine delayed release (pH>6.0), Eudragit-L, Degussa Rohm
  - mesalamine extended release (polymer core of slow-release mesalamine; pH 6.0), Apriso, Salix
  - Free 5-ASA (mesalamine) dosage can be maximized to 4.8 to 6.0 g daily, equivalent to a triple dose of sulfasalazine (12 g) with significantly less toxicity.
  - Lialda is a 1.2-g tablet that is a high-dose delayed-release pH-dependent mesalamine formulation. Once-daily is between 2.4 and 4.8 g (4 tablets).
  - Apriso once-daily 1.5-g granulated delayed and extended mesalamine (4, 0.375-g capsules) travels in solution.
  - A pH-dependent delivery system is indicated in ileocolonic disease.

- **Colonic flora-dependent, azo-bonded:**
  - sulfasalazine, Azulfidine, Pfizer
  - sulfasalazine delayed release, Azulfidine EN-Tabs, Pfizer
  - balsalazide disodium, Colazal, Salix
  - olsalazine sodium, Dipentum, Pfizer
  - 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-aminoazobenzyl-b-alanine to 5-ASA; sulfasalazine consists of 5-ASA bonded to sulfapyridine.
  - 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 new high-dose, 11-g balsalazide tablet (Salix) will allow for lower pill burden and twice-daily dosing.
  - Indicated for patients with universal and distal colitis.

- **Topical/rectal formulations:**
  - mesalamine suppositories, Canasa, Axcan Pharma
  - mesalamine enema, Rowasa, Alaven
  - Rectal preparations include 5-ASA suspensions (4-g mesalamine enema and 500-mg mesalamine suppositories) instilled directly into the rectum.
  - Advantages of topical preparations include direct exposure to diseased mucosa.
first head-to-head trial comparing an equimolar dose of balsalazide (6.75 g) with pH-dependent mesalamine (2.4 g) showed superior efficacy of balsalazide in patients with new-onset left-sided UC (62% vs 37%) and shorter time to response (10 vs 25 days). Right-sided UC also responded more favorably to balsalazide, although the difference was less significant than with left-sided disease. 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. Patients with right-sided UC treated with balsalazide had less rectal bleeding, better sigmoidoscopic-evident healing, and improved stool frequency. High-dose balsalazide 11-g tablets are being evaluated for twice-daily dosing (3 tablets or 3.3 g, bid).

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. The investigators concluded that at week 8, rates of remission were similar for all 3 treatment groups, as were the safety profiles. The primary difference between equimolar doses of balsalazide (6.75 g) and mesalamine (2.4 g) appears to be the time to symptom resolution (10 vs 25 days). The more rapid onset of action of balsalazide might be related to greater 5-ASA delivery to the colon from the azo-bonded delivery system, based on the observation that patients receiving mesalamine 2.4 g per day had significantly higher steady-state plasma levels of 5-ASA and its N-acetylated metabolite at 2 weeks than did patients receiving balsalazide 6.75 g per day (4.5-fold and 2.5-fold, respectively). This finding suggests precolonic (ileal) 5-ASA absorption 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 comparing 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) 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 receiving balsalazide had significantly higher mean mucosal concentrations of 5-ASA than patients receiving pH-dependent mesalamine. Because of the predominance of left-sided disease, the combination of oral and topical aminosalicylates is critical in inducing and maintaining remission. Safdi et al elegantly demonstrated that although topical mesalamine was more effective than oral in left-sided UC, the combination of 2.4 g of oral mesalamine and mesalamine enemas produced earlier and more complete cessation of rectal bleeding. For maintenance of remission for patients with UC, D’Albasio et al found that the combination of 1.6 g of oral mesalamine with twice-weekly mesalamine enemas was superior to oral therapy alone (61% vs 31%, respectively). Topical mesalamine (enemas and suppositories), used as infrequently as twice per week, is effective in maintaining remission in patients with distal colitis.

In another study, Biddle et al established that 75% (9 of 12) of patients randomized to receive mesalamine enemas remained in remission at 1 year, whereas 85% (11 of 13) of patients on placebo had relapsed by 16 weeks. Similarly, mesalamine suppositories maintained long-term remission in patients with ulcerative proctitis. By 12 and 24 months, respectively, 86% and 89% of placebo-treated patients had relapsed, compared with 32% and 46% of patients treated with mesalamine suppositories. 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.

Campieri et al demonstrated that mesalamine suppositories were effective in inducing remission in patients with ulcerative proctitis (distal colitis up to 20 cm). In that study, 74% of patients receiving mesalamine suppositories (1.5 g) achieved clinical remission at 4 weeks, compared with only 39% of patients receiving placebo.

The pH-sensitive 5-ASAs were evaluated in a placebo-controlled trial in patients with mild to moderate UC. Of patients receiving 4.8 g of mesalamine, 24% showed complete remission, compared with 9% of patients receiving 1.6 g of mesalamine and 5% receiving placebo. Partial response was noted in 50% of patients in the high-dose mesalamine group, compared with 18% for the low-dose group and 13% for placebo.

The ASCEND II trial found 4.8 g of delayed-release mesalamine (Asacol, Proctor & Gamble) to be superior to 2.4 g in moderate UC with response rates of 72% and 59%, respectively; remission rates were similar at 24%. 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 mild to moderate UC. In ASCEND III, the response rate was 70% at 6 weeks for patients taking 4.8 g of Asacol (6 tablets at 800 mg each), compared with 66% for those taking 2.4 g (6 tablets at 400 mg each).

A high-strength formulation of 5-ASA, multimatrix (MMX) mesalamine (Lialda, Shire), given once or twice daily has been shown 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 tablet at 1.2 g each, twice daily; 2.4 g/d) and once-daily (4 tablets at 1.2 g each, once daily; 4.8 g/d) administration. Lichtenstein et al showed that after 8 weeks of treatment, significantly greater percentages of patients taking MMX mesalamine achieved clinical and endoscopic remission 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). MMX mesalamine given once or twice daily was well tolerated and demonstrated efficacy for the induction of clinical and endoscopic remission in patients with mild to moderately active UC. Increasing the dose of Lialda to the high dose of 4.8 g per day for 8 additional weeks resulted in almost 60%
of patients with active mild to moderate UC achieving clinical and endoscopic remission and symptom resolution with a median time of 15 days.\textsuperscript{45} MMX mesalamine, 2.4 g per day either once or twice daily, resulted in maintenance of clinical and endoscopic remission.\textsuperscript{46}

In a recent dose-ranging study evaluating the optimal dosing of a novel granulated 5-ASA for inducing remission in mild to moderate active UC, the remission rate was 66% for patients taking 1 g 3 times per day (3 g/d), 50% in those taking 0.5 g 3 times per day (1.5 g/d), and 55% in those taking 1.5 g 3 times per day (4.5 g/d).\textsuperscript{47} Although there was no placebo arm in this study, there were high clinical remission rates in all 3 dose schedules. With the exception of endoscopic improvement, which was better in the group taking 3 g per day than in the group taking 1.5 g per day, no significant differences were observed in the 3 treatment groups. These findings suggest that the novel delivery mechanism of granulated mesalamine may allow for effective dose escalation. In another study, mesalamine granules given at 3 g once daily was found to be as safe and effective as 60% who maintained remission on placebo.\textsuperscript{49} Dose escalation with 1.5 g per day of granulated mesalamine delayed relapse rates between placebo and treatment groups.\textsuperscript{54} However, the analysis showed that mesalamine treatment significantly decreased the relapse rates in patients with limited ileal disease of long duration.\textsuperscript{54}

**Combining Oral Agents**

Although there are no studies evaluating the combination of oral 5-ASA drugs, we can begin to debate the virtues of combinatorial strategies in an individual patient who fails to respond to mesalamine monotherapy or 5-ASA prodrug monotherapy. 5-ASA nonresponders may benefit from a combination of pH-polymer-coated mesalamine, moisture-dependent mesalamine, and azo-bonded 5-ASA preparations (sulfasalazine, olsalazine, and balsalazide). A flexible dosing schedule, in which the patient actively modifies the combination therapy based on clinical improvement, may shorten the time to response. Lastly, a flexible dosing schedule combining 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 the individual patient not responding to the initial 5-ASA therapeutic choice, doses may be maximized 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:**

**Approaches to 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, infliximab—and even surgery—may be debated. Approximately 30% of patients treated with 5-ASA agents are deemed nonresponders. These include patients who may be allergic, intolerant, nonadherent,\textsuperscript{55} underdosed, or truly refractory to 5-ASA treatment. Allergies or intolerance to 5-ASA agents may be diagnosed in patients in whom high-grade fevers develop or who, on careful questioning, seem to worsen on 5-ASA treatment. Discontinuation of therapy in these patients paradoxically improves their condition.

Patients who respond to 5-ASA therapy may be distinguished from nonresponders on the basis of differences in clinical characteristics (mucosal or transmural inflammation, fistulizing, or stricturing CD), anatomic distribution (UC: proctitis, distal ulceration, or colitis; CD: ileal, ileocolonic, or colonic), or metabolic and signaling pathways.

**Ulcerative Colitis**

**Steroids.** Steroids have been the mainstay of treatment for inducing remission in patients not responding to 5-ASA preparations, and for patients with moderate to severe UC. Although steroids induce remission effectively, they are not effective in maintaining remission.
Furthermore, steroid dependence should not be confused with maintenance of remission. 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 also are effective in treating distal disease, although they are less effective than rectal preparations of mesalamine. Furthermore, they have been associated with mild side effects (approximately 10% of a 100-mg dose of hydrocortisone is absorbed, and therefore 10 mg of hydrocortisone is absorbed systemically).

**Probiotics.** A small study showed no significant benefit in maintenance of steroid-induced remission with the use of probiotics. Shanahan et al tested 2 probiotics—*Lactobacillus salivarius* and *Bifidobacterium infantis*—in patients with UC within 1 month of steroid-induced remission. In contrast to previous studies in animal models, these probiotics showed no benefit compared with placebo. Notably, the probiotics were initiated after patients were on steroids, raising the question of how patients would have reacted had the probiotics been initiated before steroid therapy. Perhaps steroid use has a negative effect on the microflora of the gut, and the earlier use of probiotics could decrease steroid dependency.

**6-Mercaptopurine/Azathioprine.** 6-MP and AZA have proven efficacy in the induction and maintenance of remission in patients with steroid-dependent UC. During a 5-year period, 65% of patients with UC were maintained in remission while on continued 6-MP therapy. 6-MP and AZA are used in both CD and UC. Toxicity includes 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. It should be remembered that pancreatitis is an idiosyncratic reaction and precludes any future therapy with 6-MP or AZA. In contrast, gastrointestinal intolerance with 6-MP may be avoided with AZA, and vice versa. Nausea with either agent can sometimes be avoided by administering the dose 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 rates of TPMT metabolism favor the production of the inactive metabolite 6-MMP, and less of the active and potentially toxic metabolite 6-thioguanine (6-TG). An absence or a low level of TPMT activity produces the active metabolite 6-TG, leading to potential bone marrow suppression, which can be minimized by reducing the dose of 6-MP/AZA. In contrast, normal or high TPMT levels suggest that clinicians may initiate full-dose, weight-based 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 and correcting a common error, which is to underdose 6-MP or AZA. 5-ASA compounds and furosemide also may inhibit TPMT, thereby leading to higher levels of active 6-TG. Measuring 6-TG levels is helpful in patients who are not responding to therapy 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).

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 for this disease remains low.

Data support the safety of 6-MP therapy during pregnancy. A study concluded that 6-MP taken before and at conception, and also during pregnancy, is not associated with increased prematurity, spontaneous abortion, congenital abnormalities, neonatal and childhood infections, or neoplasia. Continued follow-up studies evaluating the long-term toxicity of 6-MP and AZA are indicated.

**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 anastomosis because of concerns about the 30% to 50% risk for postoperative pouchitis and decreased fertility. The treatment and management of pouchitis are addressed in the section on surgical treatment.

Of the 80% of patients with medically refractory UC
who respond to 4 mg of IV cyclosporine per kilogram within 7 to 14 days, more than half ultimately require colectomy. 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 to the therapeutic regimen, underscoring the role of cyclosporine as a bridge to either 6-MP or AZA maintenance therapy. Because of concerns about the nephrotoxicity, encephalopathy, and immunosuppression associated with cyclosporine, it is not an effective drug for maintaining remission.

**Infliximab.** 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. The researchers concluded that patients with moderately to severely active UC 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 receiving placebo.

**When All Else Fails: Surgery for Medically Refractory UC.** Despite aggressive medical therapeutic optimization, UC remains a surgical disease. As many as 30% to 40% of patients with UC eventually require colectomy for indications of severe activity, chronic activity, dysplasia, or cancer. Nevertheless, acute or chronic pouchitis may develop after colectomy in 15% to 50% of patients with UC. Although 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, metronidazole is the treatment of choice for chronic pouchitis. Patients with chronic pouchitis may require long-term, low-dose ciprofloxacin and metronidazole therapy, or treatment with probiotics such as VSL3. In a controlled study by Gionchetti et al, 100% of the patients with pouchitis treated with antibiotics relapsed, compared with only 15% of the patients treated with VSL3. Additionally, all patients treated with VSL3 relapsed within 3 months after discontinuation of the probiotic. When chronic pouchitis debilitates a patient, 5-ASA preparations, steroids, immunomodulators, and even infliximab may be required. Rarely is pouch excision and conversion to a Brooke ileostomy required. In selected cases, ileal pouch advancement should be considered as a surgical alternative to pouch excision.

**Crohn’s Disease**

When there are no other options, conventional steroids are appropriate and currently recommended by the American Gastroenterological Association for inducing remission in patients with relatively moderate to severe CD who have not responded to 5-ASA therapy. Alternatives to conventional steroids now include 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 strictureing and fistulizing.

Furthermore, a comparison of early immunosuppression combined with infliximab induction versus conventional early steroids showed that top-down immunosuppression and infliximab allowed patients to continue to avoid steroids at the end of 2 years and most importantly, was associated with 73% mucosal healing, compared with only 30% mucosal healing in the conventional step-up steroid 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, methotrexate, 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.

**Antibiotics.** The rationale for using antibiotics in CD is related to the concept that environmental triggers that alter indigenous luminal bacteria (traveler’s diarrhea, gastroenteritis) or mucosal barrier function (acute infections, nonsteroidal anti-inflammatory drugs) increase mucosal inflammation and permeability. Metronidazole is effective for the induction and maintenance of remission in patients with perianal disease, and also for the postoperative prevention of endoscopic and clinical recurrences (when given for 3 months following ileal resection). 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. Rifaximin is an orally administered, topically active nonabsorbable antibiotic with proven efficacy in traveler’s diarrhea. It also may prove to be effective for the induction and/or maintenance of remission in patients with CD.

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

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).
A recent pharmacoeconomic study evaluating the impact of continuous steroid use (>3 months) demonstrated significant costs for society and third-party payers. In steroid-dependent patients (>6 months of steroids), short-term infliximab was ineffective as bridge therapy for AZA maintenance in both AZA-naive and AZA-experienced patients after 4 years.

Results from a controlled study comparing early administration of infliximab and azathioprine versus conventional step-up therapy revealed superior mucosal healing, more rapid remission, and higher remission rates in patients treated with the top-down approach.

**Oral Budesonide in Active Crohn’s Disease.** Oral budesonide is a topically active, rapidly metabolized steroid that is released in the ileum and right side of the colon. An optimal response to 9 mg of budesonide per day occurs within 10 days after administration (3, 3-mg tablets every morning). Additionally, 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.

Although budesonide at a dose of 3 to 6 mg prolongs the time to relapse in patients with medically induced remission, it is not effective in maintaining remission at 1 year. 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 of remission with immunomodulator (6-MP/AZA) therapy. However, in patients with mild ileocolitis who are 5-ASA-naive, the use of budesonide should be debated. Using budesonide as first-line therapy for mild ileocolitis may result in the overuse of immunomodulators to maintain remission.

**6-Mercaptopurine/Azathioprine.** 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. In addition, treatment with 6-MP completely closed 31% of fistulas, compared with a 6% complete closure rate in the placebo group. However, the time to response was delayed; more than 3 months were required to achieve clinical improvement in 50% of patients.

In a 15-month, double-blind, controlled maintenance study, 42% of patients receiving AZA (2.5 mg/kg) remained in remission, compared with 7% in the placebo group. In children with CD, the early introduction of 6-MP therapy was found to achieve and maintain steroid-free remission; only 9% of children relapsed while on 6-MP therapy, compared with 47% of controls. Further studies to support the use of 6-MP before the initiation of steroid therapy are warranted.

The importance of assessing thiopurine methyltransferase (TPMT) phenotype (the number of enzymes) and the identification of a subset of patients with suboptimal levels of 6-TG (indicating 6-MP resistance) is increasingly recognized (Figure 4). In patients who have high TPMT activity with preferential production of the 6-MMP metabolite, low-dose allopurinol (a xanthine oxidase inhibitor) appears to be an effective means to shunt metabolism toward 6-TG.

An excess risk for lymphoproliferative disease has been observed in patients receiving AZA, with a fatal outcome in almost half the cases and frequent association with Epstein-Barr viral infection.

**Methotrexate.** After 4 months of methotrexate therapy (25 mg IM weekly) for active CD, 39% of patients achieved clinical remission, compared with 19% in the placebo group. In a follow-up study evaluating methotrexate for maintenance of remission, 65% of patients receiving methotrexate (15 mg IM weekly) were in remission, compared with 39% of patients receiving placebo. In steroid-dependent patients with a forced steroid taper over 14 weeks, there was no difference between methotrexate in combination with infliximab or infliximab alone, suggesting that with regularly scheduled infliximab monotherapy, there is no need for immunosuppression.

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

**Infliximab.** Infliximab has been shown to be a highly effective agent for the treatment of moderately to severely active, medically refractory, inflammatory and fistulizing CD. Four weeks after a single infusion of 5 mg/kg of infliximab, 81% of patients had a clinical response, compared with 17% of patients in the placebo group. The role of infliximab in maintenance therapy continues to be defined. In the ACCENT I trial, a large, multicenter, controlled study of maintenance infliximab therapy given every 8 weeks, 39% and 45% of patients receiving 5 and 10 mg/kg of infliximab, respectively, were in clinical remission at week 30, compared with 21% of patients receiving placebo. In another controlled trial, 5 mg/kg of infliximab, given in 3 doses, completely closed fistulas for a median time of 3 months in 46% of patients and achieved a 50% reduction in fistula drainage in 62% of patients.

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, 63.5% and 55.8% of patients who received infliximab every 8 weeks achieved clinical response and were in clinical remission, respectively, and did not require dose adjustment. At the end of 1 year, almost 50% of children receiving infliximab every 8 weeks were in remission and no longer on steroids.
compared with only 17% of children receiving infliximab every 12 weeks. 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 TREAT registry data found no increased risk with infliximab for CD.

**Adalimumab.** In February 2007, adalimumab was approved 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 was shown to induce remission more frequently than placebo. Among patients who initially responded to adalimumab, Colombel et al reported significantly higher rates of remission with adalimumab versus placebo at 1 year. In patients with CD for less than 2 years, approximately 50% remained in remission more than 1 year after receiving 40 mg of adalimumab subcutaneously every other week or every week.

**Certolizumab.** Certolizumab pegol is a pegylated Fab’ fragment of a humanized monoclonal antibody that neutralizes TNF-α. It was approved by the FDA in April 2008 for the 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, as compared with placebo, but no significant improvement in remission rates. In addition, patients who had a response to induction therapy with certolizumab were more likely to have maintained response and remission at 26 weeks with continued treatment compared with a switch to placebo.

The results from the induction phase of the PRECISE 2 trial compared favorably with other monoclonal anti-TNF induction studies. The 6-week response rates of approximately 66% of patients in the study and remission rates of 40% were unaffected by concomitant immunosuppressants or corticosteroids. Long-term data of certolizumab (at 52 and 54 weeks) suggest that 400-mg subcutaneous injections given monthly are well tolerated with low anti-double-stranded DNA—3.2% in PRECISE 3 and 2.7% in PRECISE 4—possibly because of the low apoptosis rates associated with certolizumab. In more than 900 patients treated with certolizumab for 1 year, the incidence of infections and malignancy is similar to other anti-TNF agents. In the WELCOME study, nearly 66% of patients who had lost response or were intolerant to infliximab responded to induction with certolizumab at 0, 2, and 4 weeks, with maintenance every 2 or 4 weeks. In addition, almost 40% of those patients achieved remission on certolizumab.

More than 66% of patients maintained remission with 400 mg of certolizumab pegol over 26 weeks with disease duration less than 1 year, contrasted with only 44% with disease duration greater than 5 years. Combination Anti-TNF and Immunosuppression (AZA, 6-MP, Methotrexate). Steroid-exposed immunosuppression-naïve patients with moderate to severe CD treated with infliximab monotherapy or a combination of infliximab and AZA were more likely to achieve and maintain steroid-free remission with mucosal healing at the end of 6 months than patients treated with AZA alone. The average duration of disease in the SONIC trial was 2 years and the AEs—including serious infections—were similar in all treatment groups. Interestingly, when steroid-free clinical remission was stratified by C-reactive protein (CRP), 35% and 40% of patients with less severe disease (CRP<0.8 mg/dL) were in clinical remission on AZA or infliximab, respectively, contrasted with 28% and 48% of patients with more severe disease (CRP>0.8 mg/dL). It is important to recognize that this was an early intervention trial (average disease duration of 2 years) and reflects only 6 months of data. In select patients with short-duration, severe disease, combination therapy for 6 months was more effective than monotherapy. The SONIC trial does not address top-down steroid strategy—that is, steroids and weight-based AZA or 6-MP early in the course of aggressive CD—and also does not address AEs related to combination infliximab and AZA in long-standing CD.

**Natalizumab.** Approved by the FDA in January 2008, natalizumab is a humanized IgG4 monoclonal antibody against α4-integrin also used to treat multiple sclerosis (MS). It has demonstrated 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 natalizumab-treated patient with CD with prior exposure to AZA and steroids, and an underlying lymphopenia. Subsequently, no new cases of PML were identified in patients treated with natalizumab in clinical trials, and a recent report suggested a risk for PML of roughly 1 in 1,000 patients treated with natalizumab for a mean of 17.9 months. Currently, more than 45,000 patients (mostly with MS) have been treated, with rare new cases of PML reported. There have been some reports of liver abnormalities.

A recent randomized, placebo-controlled trial of natalizumab induction therapy in patients with CD reported response and remission at week 8 that persisted through week 12; both response and remission rates were superior to those in patients taking placebo at weeks 4, 8, and 12 of the study, demonstrating an early and sustained efficacy of natalizumab as induction therapy. Natalizumab was well tolerated in this
study. Because PML was associated with combination therapy in patients taking natalizumab, this therapy has been approved by the FDA as monotherapy in patients with CD.

Post hoc subgroup analyses of the ENACT 2 and ENCORE maintenance trials found consistently higher induction remission rates for nearly 25% of patients with short-duration CD (<3 years). Almost 33% of patients in the ENCORE trial were considered infliximab failures; 38% of these patients achieved a sustained response through weeks 8 and 12, compared with 17% of those on placebo. Remission rates at 12 weeks were unaffected by concomitant immunosuppressants for nearly 40% of patients. Two-thirds of patients in the ENCORE trial (randomized 1:1 to receive 300-mg natalizumab infusions at 0, 4, and 8 weeks) were not taking immunosuppressants.

**Novel Biologics.** 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, teduglutide was safe and effective for inducing remission in patients with moderate to severe CD as early as week 2, with an increase in remission rates at week 8, suggesting a durable response. AEs were generally self-limited and mild in nature. Vedolizumab is a monoclonal antibody targeting the α4β7 integrin, which selectively inhibits lymphocyte recruitment in the gastrointestinal tract. Vedolizumab (MLN-0002) at 2mg/kg induced a significantly greater clinical remission rate in patients with CD compared with placebo (37%). Ustekinumab is a monoclonal antibody against the P40 subunit of IL-12/23 and induced a clinical response in patients with moderate to severe CD, especially infliximab–primary (never responded) and secondary (attenuated response) nonresponders.

**Surgery.** Like UC, CD remains a surgical disease, with 70% to 80% of patients requiring surgery during their lifetime. Laparoscopic ileocolic resection has shortened recovery time and length of hospital stay for patients with medically refractory CD. Earlier surgical intervention may be of benefit with minimally invasive laparoscopic techniques, as well as novel bowel-sparing strictureplasty. The combination of infliximab and surgery for perianal disease (including seton placement) closed perianal fistulas in 68% of patients and reduced the rate of recurrent abscesses.

The annual incidence of clinically significant postoperative recurrence is 8% to 10%; strictureing disease tends to develop more slowly, and fistulizing disease tends to recur faster. 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. 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.

Postoperative recurrence may be prevented by the addition of 5-ASA, 6-MP/AZA, VSL3, or infliximab. Postoperative infliximab significantly lowered endoscopic recurrence at 1 year in complex fistulizing CD. Only 9% of patients who had undergone an ileocolonic resection had documented endoscopic recurrence after 1 year of postoperative infliximab (3-dose induction followed every 8 weeks for 1 year). AEs were similar in infliximab and placebo groups (the placebo group did include patients on AZA and 6-MP). Each postoperative therapy is more effective than placebo in preventing clinical and/or endoscopic recurrences, although additional prospective studies are needed to establish duration of postoperative maintenance and to define interval of postoperative endoscopic evaluations.

**Conclusion**

Identifying select patients with moderate to severe IBD who will benefit from early intervention—immunomodulator and/or biologic therapy—will result in minimizing or avoiding steroids and may slow or reverse the progression of immune-mediated inflammation of the gut. The recent expansion of the indications for anti-TNF and anti-integrin therapies and the demonstrated success of the earlier top–down approach (infliximab and immunosuppressants in steroid-naïve patients) suggest that earlier use of immunomodulators and/or biologic agents in patients with short-duration disease (<2 years) may prove to be steroid-sparing and may favorably alter the inexorable progression of the natural history of UC toward colectomy and of CD toward strictureting and fistulizing structural damage. As we introduce immunosuppressants and/or biologic agents at an earlier stage (as induction and maintenance therapy in steroid-naïve patients or after short-term steroids), we may see less AEs than when we layer immunosuppressants and biologics on top of prolonged steroids.

Until steroid use is limited, adding immunosuppressants and biologics puts a small group of patients at risk for IBD-associated immune deficiency and clear guidelines for preventing opportunistic infections and registries for documenting lymphoma and cancer risk in patients with moderate to severe IBD need to be established.

In selected patients with moderate to severe disease, an earlier aggressive approach will be indicated; in other patients with mild to moderate disease, stepping back and challenging the diagnosis, decreasing medication doses, and stressing adherence to therapeutic regimens are in order. Identifying immunologically vulnerable subsets of patients with emerging serologic markers, biomarkers, and ultimately genotyping may allow for stratification of therapeutic responses and individualized medicine.

Decoding of the human genome is redefining the
science of individuality, reminding us that less than 0.1% of our DNA is responsible for disease susceptibility and therapeutic response.146-149 Although we are poised to recognize the potential for genotyping to inform our therapeutic options, we are far from the routine use of genotyping in selection of optimal therapies. We are at the threshold for genotyping both individual patients and bacteria, which will lead to a greater understanding of the pathobiology of IBD and improving clinical outcomes.150

Until the science of the human genome and microbiome translates into individualized medicine, predicting the outcome of disease progression may best be achieved with personal risk assessment (including post-operative endoscopic evaluation or emerging biomarkers) and stratification of therapy (earlier aggressive intervention in more severe patients and dose de-escalation in patients with less severe disease). We recognize that in selected patients with moderate to severe disease, early intervention with immunosuppression or biologic therapies—and limited steroids—may favorably affect the natural history of IBD and move treatment from symptom-oriented step-up to prevention-oriented early intervention strategies.

References


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