Crohn's and Colitis at the Crossroads: Part 2
Redefining the Pyramid: A New Paradigm For 5-ASA Nonresponders

For patients with inflammatory bowel disease (IBD), the optimal treatment strategy depends on the location, severity, and extraintestinal manifestations of their disease. Treatment is individualized according to symptomatic response and predicated on an escalating step-up approach in which the least toxic medications are used as first-line therapy.1,2

Although 5-aminosalicylic acid (5-ASA) compounds have been considered the cornerstone of induction therapy for both ulcerative colitis (UC) and Crohn's disease (CD), in selected cases, the earlier use of more potent medications, such as budesonide (Entocort, AstraZeneca), azathioprine (Imuran, GlaxoSmithKline; Azasan, Salix), 6-mercaptopurine (Purinethol, GlaxoSmithKline), infliximab (Remicade, Centocor)—and even surgery—may be debated (Figure 1, page 52).

Nonresponders to 5-ASA

Approximately 30% of patients treated with 5-ASA agents are deemed nonresponders. These include patients who may be allergic, intolerant, nonadherent, underdosed, or truly refractory to 5-ASA treatment (Figure 2, page 53). 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.

Targeting Disease Location

In both distal and universal colitis, patients are bothered by symptoms of an inflamed, irritable distal colon (urgency, increased defecation, tenesmus, or hard stools), suggesting that 5-ASA release should be targeted to the left side of the colon. Often, patients are reluctant to use a combination...
of oral and topical 5-ASA products initially. Therefore, starting patients who have distal UC with 5-ASA suppositories and/or enemas and then stepping up to oral 5-ASA agents are recommended. In patients with more extensive UC, starting therapy with oral 5-ASA agents and stepping up to rectal 5-ASA agents are recommended.

First-line oral therapy (Table 1; Figure 3, page 54) for UC includes 5-ASA prodrugs—sulfasalazine (Azulfidine, Pfizer), olsalazine (Dipentum, Celltech), and balsalazide (Colazal, Salix)—and free 5-ASA—mesalamine (Asacol, Procter & Gamble; Pentasa, Shire US). Patients with UC who fail to respond to Asacol therapy at 2.4 g per day may be switched to high-dose Asacol (4.8 g per day),5 with or without topical therapy,6 or switched to a 5-ASA prodrug.

Patients with UC should not be deemed 5-ASA nonresponders until they have failed dose-escalation regimens, including high-dose Asacol (4.8 g per day) or Pentasa (4.0 g per day), as well as the combination of oral 5-ASA agents and mesalamine 4.0 g enemas (Rowasa, Solvay).6 In addition, clinical studies suggest that patients should not be considered 5-ASA nonresponders until they have attempted balsalazide therapy. In about 60% of patients, balsalazide 6.75 g, which is equivalent to 5-ASA 2.4 g, can help “salvage” patients who have failed to respond to Asacol (4.8 g per day) and can rescue 30% of patients who have failed on a combination of high-dose Pentasa (4.0 g per day) and Asacol (4.8 g per day) with or without steroids within a median of 7 days.7 Balsalazide salvage therapy may represent an important side step in the treatment pyramid, precluding the need to step up to steroid therapy in selected patients. Further controlled trials are warranted to evaluate balsalazide not only as a salvage therapy but also for its possible steroid-sparing effect, and to compare high-dose Asacol (4.8 g; equivalent to 5-ASA 2.4 g) with standard-dose balsalazide (6.75 g; equivalent to 5-ASA 2.4 g) and high-dose balsalazide (13.5 g; equivalent to 5-ASA 4.8 g) in patients with universal and distal colitis.

Although mesalamine optimization strategies include both mesalamine suppositories (Canasa, Axcan Scandipharm) and enemas to induce and maintain remission, a common error is not to use these topical agents once step-up therapy is initiated. Optimized 5-ASA treatment should be carried all

<table>
<thead>
<tr>
<th>LOCATION OF DISEASE</th>
<th>COLITIS/ FISTULIZING CROHN’S DISEASE</th>
<th>DUODENITIS/ JEJUNITIS/ILEITIS</th>
<th>PROCTITIS</th>
<th>DISTAL COLITIS</th>
<th>ULCERATIVE/INDETERMINANT COLITIS</th>
<th>CROHN’S COLITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ULCERATIVE COLITIS</strong></td>
<td>Surgery</td>
<td>TPN</td>
<td>Infliximab</td>
<td>Cyclosporine</td>
<td>Tacrolimus</td>
<td>Inflimiximab</td>
</tr>
<tr>
<td></td>
<td>I.V. steroids</td>
<td>Methotrexate</td>
<td>Asacol (4.8 g)</td>
<td>Pentasa (4.0 g)</td>
<td>Asacol (2.4 g)</td>
<td>Budesonide</td>
</tr>
<tr>
<td></td>
<td>Oral Steroids</td>
<td>Oral Steroids or Budesonide</td>
<td>5-ASA Prodrugs</td>
<td>5-ASA Prodrugs</td>
<td>5-ASA Prodrugs</td>
<td>Antibiotic Therapy: Ciprofloxacin and Metronidazole</td>
</tr>
<tr>
<td></td>
<td>Topical Mesalamine and Steroids</td>
<td>6-MP/AZA</td>
<td>Sulfa-salazine (4.0 g=1.8 g 5-ASA)</td>
<td>Olsalazine (3.0 g=3.0 g 5-ASA)</td>
<td>Balsalazide (6.75 g=2.4 g 5-ASA)</td>
<td><strong>MILD</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asacol (4.0 g)</td>
<td>Pentasa (4.0 g)</td>
<td>Asacol (4.8 g)</td>
<td>6-MP/AZA</td>
</tr>
<tr>
<td><strong>CROHN’S DISEASE</strong></td>
<td><strong>SEVERE</strong></td>
<td><strong>MODERATE</strong></td>
<td>Inflimiximab</td>
<td>Cyclosporine</td>
<td>Inflimiximab</td>
<td><strong>Invert the Pyramid</strong></td>
</tr>
<tr>
<td></td>
<td>Consider surgery before infliximab.</td>
<td><strong>Invert the Pyramid</strong> Consider using infliximab/cyclosporine before I.V. steroids.</td>
<td><strong>Invert the Pyramid</strong> Consider using 6-MP/AZA before oral steroids.</td>
<td><strong>Invert the Pyramid</strong> Consider using 6-MP/AZA before oral steroids or budesonide.</td>
<td><strong>Invert the Pyramid</strong> Consider using infliximab/budesonide.</td>
<td><strong>Invert the Pyramid</strong> Consider using 6-MP/AZA before oral steroids.</td>
</tr>
</tbody>
</table>

**Figure 1. Inflammatory bowel disease treatment pyramid.**

AZA, azathioprine; C, Canasa; I.V., intravenous; 6-MP, 6-mercaptopurine; R, Rowasa; TPN, total parenteral nutrition
the way up the pyramid. Topical 5-ASA should remain an adjunct to more potent therapy.

**Maintaining Remission**

After induction of remission, the goal is to maintain remission and avoid long-term steroid toxicities and surgical intervention. One approach is to recommend that the dose of mesalamine used to induce remission be the same dose used to maintain remission. However, there is no consensus regarding maintenance dosing, and reduced dosing regimens have been found to be equally effective for all of the 5-ASA compounds.

The role of the 5-ASA compounds in maintaining remission in UC is well established. Whether 5-ASA maintenance prevents progression of disease or is chemopreventive (ie, prevents dysplasia and colon cancer) in UC (Table 2, page 54; Figure 4, page 55) remains an open and intriguing clinical question supported by some retrospective studies and, conversely, refuted by at least 1 study. Although 5-ASA is a safer alternative to steroids or immunomodulators, efficacy for induction of remission in CD is limited by only a 40% remission rate in patients given high-dose mesalamine (Pentasa, 4.0 g). The use of higher dose mesalamine (6.0 g) may offer CD patients the safety of 5-ASA with the efficacy of higher dosing. Its role in maintaining remission in CD is more controversial.

**Alternatives to 5-ASA: Approaches To 5-ASA Nonresponders**

A brief review follows of the current literature on the efficacy of the various treatments for UC, organized by medication type.

**A. Ulcerative Colitis**

1. 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 adverse events, including the development of avascular necrosis of the hip, osteoporosis, cataracts, glaucoma, diabetes, acne, and emotional disturbances. Rectal steroid preparations are also effective in treating distal disease, although they are less effective than rectal preparations of mesalamine, such as Rowasa and Canasa. Furthermore, they have been associated with mild side effects (approximately 10% of a 100-mg dose of hydrocortisone in an enema is absorbed, and therefore 10 mg of hydrocortisone is absorbed systemically).

2. 6-Mercaptopurine/azathioprine. 6-Mercaptopurine (6-MP) and azathioprine (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 (~2%), pancreatitis (~3%), hepatitis (0.3%), and infectious complications (7-3%), which may be attributed to concomitant steroid use. It should be remembered that pancreatitis is an idiosyncratic reaction and precludes any future rechallenge 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 drug at bedtime.

6-MP and its prodrug AZA are metabolized by thiopurine methyltransferase (TPMT) to inactive 6-methylmercaptopurine (6-MMP) (Figure 5, page 56). 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 patients may initiate full-dose 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 may also 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. 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.

The results of a recent study support the safety of 6-MP therapy during pregnancy. The 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.

**Table 1. Comparison of 5-ASA Compounds**

<table>
<thead>
<tr>
<th>Generic/Brand Name of Compound</th>
<th>Individual Dose</th>
<th>Recommended Daily Dose</th>
<th>Equivalent Dose of Free 5-ASA</th>
<th>Mole-for-Mole Equivalence (2.4 to 2.5 g Free 5-ASA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-ASA PRODRUGS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sulfasalazine (Azulfidine)</td>
<td>500 mg</td>
<td>4.0 g</td>
<td>1.8 g</td>
<td>6.0 g</td>
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<tr>
<td>Olsalazine (Dipentum)</td>
<td>250 mg</td>
<td>3.0 g</td>
<td>3.0 g</td>
<td>2.5 g</td>
</tr>
<tr>
<td>Balsalazide (Colazal)</td>
<td>750 mg</td>
<td>6.75 g</td>
<td>2.4 g</td>
<td>6.75 g</td>
</tr>
<tr>
<td><strong>FREE 5-ASA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oral mesalamine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Asacol</td>
<td>400 mg</td>
<td>2.4 to 4.8 g</td>
<td>2.4 to 4.8 g</td>
<td>2.4 g</td>
</tr>
<tr>
<td>Pentasa</td>
<td>250 mg</td>
<td>4.0 g</td>
<td>4.0 g</td>
<td>2.5 g</td>
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<tr>
<td>Rectal mesalamine</td>
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<td></td>
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<tr>
<td>Canasa suppository</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>2.5 g</td>
</tr>
<tr>
<td>Rowasa enema</td>
<td>4 g/60 cc</td>
<td>4.0 g</td>
<td>4.0 g</td>
<td>2.5 g</td>
</tr>
<tr>
<td><strong>5-ASA, 5-aminosalicylic acid</strong></td>
<td></td>
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</tr>
</tbody>
</table>

**Failures of therapy**

- Underdosing or wrong dose
- Premature transition from induction to maintenance
- Inadequate adherence to therapy

**Failures of diagnosis**

- Crohn’s disease–like ulcerative colitis (UC)
- Refractory left-sided colitis, with or without a fecal patch
- UC with “mucin” (cryptolytic) nonneutrophilic granulomas (possibly secondary to 5-ASA allergy)
- UC with posttreatment alterations
- Ischemia
- Intercurrent infection
  1. Clostridium difficile
  2. Cytomegalovirus
  3. Amebiasis

**Figure 2. Differential diagnosis for pseudorefractory colitis.**

5-ASA, 5-aminosalicylic acid
3. 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 ileoanal anastomosis because of concerns about the 50% 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 I.V. 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, cataractophathy, and immunosuppression associated with cyclosporine, it is not an effective drug for maintaining remission.

4. Infliximab. Infliximab has been evaluated in patients with moderate to severe UC with response rates ranging from 50% to 80% and almost as effective as methylprednisolone in the almost as effective as azathioprine. In a recent randomized, placebo-controlled study, however, infliximab therapy did not relieve steroid-resistant UC. The result of an ongoing multicenter, double-blind, controlled trial, evaluating the efficacy of infliximab in inducing and maintaining remission in patients with predominantly steroid-dependent UC, will clarify the conflicting evidence regarding infliximab for the management of UC.

5. When All Else Fails: Surgery for Medically Refractory UC—ileo-Pouch Anal Anastomosis and Pouchitis. 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.

B. Crohn’s Disease

Conventional and novel steroids are appropriate for inducing remission in patients with CD who have not responded to 5-ASA therapy, and when the disease is relatively severe. Alternatives to steroids include antibiotics, immunomodulators, anti-tumor necrosis factor (anti-TNF) agents, and newer biologic agents. Anti-TNF agents elicit a rapid response (within 2 weeks after administration). Maintenance of long-term remission may be possible in select 5-ASA responders with mild disease, but many patients with moderate to severe disease require 6-MP, AZA, methotrexate, or infliximab. Currently, the evidence for the use of antibiotics for long-term maintenance therapy is anecdotal, and recent reports looking at probiotics for maintenance of remission in CD are disappointing. A brief review follows of the current literature on the efficacy of the various treatments for CD organized by medication type.

1. Antibiotics and Probiotics. 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 (Xifaxan, Salix) is a new orally administered, topi-
cally active nonabsorbable antibiotic with proven efficacy in traveler’s diarrhea. It may also prove to be effective for the induction and/or maintenance of remission in patients with CD.

2. Steroids. Almost 60% of CD patients initially treated with steroids enter 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.

3. Oral Budesonide in Active Crohn’s Disease. Oral budesonide is a topicaly active, rapidly metabolized steroid that is released in the ileum and colon. An optimal response to budesonide 9 mg per day occurs within 10 days after administration (three 3-mg tablets every morning). Additionally, studies show that budesonide is superior to high-dose mesalamine (Pentasa, 4 g per day) for the induction of remission in patients with active Crohn’s ileocolitis.55 In another study, compared with 23% of patients receiving placebo, 46% in another controlled trial, 5 mg of infliximab per kilogram, 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.

4. 6-Mercaptopurine/Azathioprine. Among patients with active CD, 67% of those treated with low-dose 6-MP (30 mg) showed overall clinical improvement, compared with 8% of patients on placebo.55,56 In addition, treatment with 6-MP completely closed 51% of fistulas, compared with a 6% complete closure rate in the placebo group. However, physicians and patients had to be patient; the time to response was delayed—with longer than 3 months required to achieve clinical improvement in 50% of patients. In a 15-month, double-blind, controlled maintenance study, of patients receiving AZA (2.5 mg/kg) remained in remission, compared with 7% in the placebo group.60 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.

5. Methotrexate. After 4 months of methotrexate therapy (25 mg IM weekly) for active CD, 59% of patients achieved clinical remission, compared with 19% in the placebo group.63 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.

6. Tacrolimus and Cyclosporine. Tacrolimus (Prograf, Fujisawa) and cyclosporine may still 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.55 In a study by Brynskov et al, 59% of patients with steroid dependence or intolerance responded to cyclosporine (7.5 mg/kg per day) over 3 months, compared with 32% in the placebo group.

7. Infliximab. Infliximab has been shown to be a highly effective agent for the treatment of moderate to severe active, medically refractory, inflammatory and fistulizing CD.54 Four weeks after a single infusion of 5 mg of infliximab per kilogram, 81% of patients had a clinical response, compared with 17% of patients in the placebo group.57 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, 59% and 45% of patients receiving 5 mg and 10 mg of infliximab per kilogram, respectively, were in clinical remission at week 30, compared with 23% of patients receiving placebo.56 In another controlled trial, 5 mg of infliximab per kilogram, 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.

8. Surgery. Like UC, CD remains a surgical disease.55,56 The annual incidence of clinically significant postoperative recurrence is 20% to 40% of patients; this disease tends to develop more slowly and fistulizing disease tends to recur faster.54 The severity of clinical postoperative recurrences can be predicted by the severity of endoscopic anastomotic lesions. According to a study by Rubin et al, endoscopically based recurrences developed in 75% of patients within 1 year after ileocolonic resection. Three years after surgery, the endoscopic recurrence rate increased to 85%, and symptomatic recurrence was noted in 54% of patients Those in whom diffuse, deep new ileal recurrences developed within a year tended to experience early symptoms and complications.73 Postoperative recurrence may be prevented by the addition of 5-ASA55-57 or 6-MP/AZA; each is more effective than placebo in preventing clinical and endoscopic recurrences, although additional prospective studies are needed.

Conclusion

Treatments for IBD are currently selected according to symptomatic response and definition of natural history. We are entering a genomie era in medicine, in which the therapeutic paradigm is shifting toward a redifinition of IBD based on molecular pathways and targets. Because of the impact of immunogenoetys, it will be possible to administer therapies that are more targeted, better tolerated, and more effective earlier in the course of disease. Identifying immunologically vulnerable subgroups of patients will allow us to invert the therapeutic pyramid, and perhaps slow—or even reverse—the progression of immune-mediated inflammation of the gut, aka IBD.

Salicylates (aspirin) are known to prevent sporadic polyps in individuals who do not have inflammatory bowel disease (IBD). Therefore, it is intuitive to study the effect of 5-aminosalicylate (5-ASA) in cancer prevention in patients with IBD.

PRO:

- A European case-control study has shown a significant reduction in cancer risk in patients with ulcerative colitis (UC); the risk for development of dysplasia was reduced by 81% (P=0.006) in patients taking 5-ASA ±1.2 g per day, and by 75% (P=0.00001) in those taking any 5-ASA.12
- Another European study showed that 5-ASA lowered the risk for colorectal cancer (CRC) by 46%.15
- Rubin reported a case-control study in which the risk for the development of dysplasia or cancer was reduced by 72%.15
- Ullman et al showed that 5-ASA ±2.0 g per day prevented the progression of indefinite to advanced neoplasia.77 However, once low-grade dysplasia (LGD) developed, it had no beneficial effect on progression to high-grade dysplasia (HGD) or CRC. Although Croog et al, in a more recent review, showed that 5-ASA use resulted in lower rates of progression to HGD and CRC, a similar trend with respect to progression to LGD fell short of significance.15

CON:

- A Canadian population-based study, avoiding referral bias, did not support 5-ASA conferring chemoprevention.15 However, this study may have been limited by the small number of patients in whom IBD-associated cancer developed, the inability to evaluate dosing of 5-ASA, and short periods of follow-up of patients on 5-ASA.

Figure 4. Is 5-ASA chemopreventive for IBD-related colorectal cancer?

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