Crohn’s Is Not a 6-Week Disease

Lifelong Management of Mild to Moderate Crohn’s Disease

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Abstract: Crohn’s disease is an idiopathic, chronic inflammatory disorder of the digestive tract with heterogeneous clinical presentations. Crohn’s is currently not a curable disease, and patients are faced with a lifetime of recurrent disease flare-ups and remissions. Management strategies for Crohn’s must therefore be targeted toward lifelong management, taking into consideration not only the short-term but also the long-term aspects of the disease. With this in mind, here we review the classifications and natural history of Crohn’s disease and discuss possible predictive factors for the disease evolution in a patient. Here we also evaluate the current preferable treatment practices, based on scientifically valid research and collective clinical experience, for the management of mild to moderate Crohn’s disease.

Key Words: Crohn’s disease classifications, natural history, management

Crohn’s Disease Classification

There is a need for the development of a classification system that would allow for the identification of patient subgroups and guide therapeutic interventions in Crohn’s disease. A standardized classification system would also aid our ability to correlate putative etiological factors, both genetic and environmental, with particular disease phenotypic characteristics. However, the wide spectrum of disease manifestations has made classification of Crohn’s problematic, and experts have struggled to classify Crohn’s disease according to anatomy as well as disease behavior.

Anatomy is a major determinant of the symptoms, clinical course, and prognosis of the disease and is therefore a key component in Crohn’s disease classification.1,2 In 29% of patients with Crohn’s disease, the disease is confined to the small intestine; in 27% of cases only the colon is involved; and in 41% of cases patients, have involvement of both the small intestine and colon.1 Thus, 70% of patients with Crohn’s disease have small bowel involvement. These different disease locations have been associated with distinct patterns of complications. In a study of 615 patients with Crohn’s disease, Farmer and coworkers found that ileocolonic disease was associated with perianal fistulas, internal fistulas, and intestinal obstruction, while colonic disease was associated with rectal bleeding, perianal fistulas, toxic megacolon, and arthritis.1 In addition, 73% of patients with ileocolonic Crohn’s disease required surgery, as compared with only 51% of patients with colonic disease. Patients in whom the disease was confined to the small intestine had the best prognosis: 51% required surgery, with intestinal obstruction as the major indication.

Disease behavior describes the biology of Crohn’s disease in relation to the occurrence of specific pathologic features and is associated with the development of complications and need for surgery. The concept of disease behavior in Crohn’s disease was first used to refer to the indication for surgery; a study by Greenstein and colleagues examined 770 patients with Crohn’s disease undergoing intestinal resection, dividing the patients into perforating or nonperforating indication groups.3 The study found that the indications for surgery tended to remain the same from the initial to subsequent operations. Seventy-three percent of perforating and 71% of nonperforating patients who underwent a second operation had the same indication for both their first and second operations. The study also found that patients with perforating disease tended to have a more rapid recurrence of disease, suggesting a correlation between perforating disease behavior and an aggressive form of Crohn’s disease, while nonperforating disease behavior correlated with an indolent form of the disease.

A recent attempt at classification, called the Vienna classification, is based on both disease behavior as well as anatomy, along with age at diagnosis (see Table 1).4 In this system, disease behavior is subclassified into inflammatory (nonstricturing nonpenetrating), stricturing, and penetrating disease. The Vienna classification has been used by several
studies to examine the evolution of disease behavior over the course of Crohn’s disease,²,⁵,⁶ as discussed below.

**NATURAL HISTORY OF CROHN’S DISEASE**

A difficulty with the Vienna classification is that Crohn’s disease behavior does not remain constant during the course of the disease. Louis and associates retrospectively examined the behavior of Crohn’s disease, using the Vienna Classification, in 297 Crohn’s disease patients over a 10-year period.⁷ The investigators found that although the location of the disease remained relatively stable over the course of the disease, disease behavior varied dramatically. While the majority (74%) of patients had uncomplicated inflammatory disease (B1) at diagnosis, very few had uncomplicated disease after 25 years of follow-up. Within 10 years, 46% of patients had changed disease behavior. The most prominent change seen was from the B1 disease behavior to either stricturing (B2) (27.1%; $P < .0001$) or penetrating (B3) (29.4%; $P < .0001$) disease. Moreover, the rate of change from B1 to either the B2 or B3 phenotype remained stable over 25 years, with approximately 25 to 33% of B1 patients changing to B2 or B3 every 5 years. These results suggest that nearly all the patients in the study population will develop either stricturing or penetrating disease over time. The study also found a correlation between ileal disease location and stricturing, and between colonic or ileocolic disease and penetrating complications.

Cosnes and associates examined the long-term evolution of Crohn’s disease behavior in a retrospective study of 2002 patients with Crohn’s disease over a 20-year period.² The authors found that after 20 years, patients in the initial cohort had an 88% risk of developing either stricturing (18%) or penetrating (70%) disease behavior. The study also attempted to identify any predictive factors for Crohn’s disease evolution, and found that the major difference in the risk of developing either a stricturing or penetrating complication could be attributed to disease location. Patients with terminal ileal disease were more prone to developing a complication: at 20 years, 94% of patients had a complication. Patients with colonic disease were at lower risk, with 78% suffering from a complication by 20 years, almost exclusively of the penetrating type. Patients with ileocolonic and upper gastrointestinal disease had intermediate behaviors. These results show that the initial location of the lesions was the determining factor of disease behavior, and that the disease activity was poorly influenced by previous disease behavior.

A later study by Louis and colleagues examined factors that may influence the progression of disease behavior, again using the Vienna classification.⁶ The authors examined 163 patients with an initial B1 phenotype and assessed changes in behavior over a 5-year period. After 5 years, disease behavior was still classified as B1 in 67.5% of patients, B2 in 11.0%, and B3 in 21.5%. The authors attempted to identify markers or factors associated with these changes and found that disease location was a critical determinant in the progression of disease behavior. Smoking was also a determinant in the progression to penetrating complications in patients, but the NOD2/CARD15 genotype was not found to be a determinant of the disease course.

However, the studies by Louis⁵,⁶ and Cosnes² may be skewed toward the group of patients with very active disease who are frequent visitors in hospitals and outpatient clinics. There is evidence that the overall clinical course of Crohn’s disease in the community can be relatively mild. Munkholm and colleagues examined the long-term disease course in an unselected group of 373 patients with Crohn’s disease over a 25-year period.⁷ Although 80% of patients had high activity at diagnosis, this value decreased to an almost stable value of 30% in the following years. A constant value of 15% had low activity, and approximately 55% could expect to be in clinical remission each year. Thus, after the first year of diagnosis, the majority of patients with Crohn’s disease in any population has mild disease activity or is in remission.

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**TABLE 1. The Vienna Classification of Crohn’s Disease**

<table>
<thead>
<tr>
<th>Age at diagnosis*</th>
<th>A1</th>
<th>&lt;40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>≥40 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location†</th>
<th>L1</th>
<th>Terminal ileum‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2</td>
<td>Colon§</td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>Ileocolon¶</td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>Upper gastrointestinal‖</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavior</th>
<th>B1</th>
<th>Nonstricturing, nonpenetrating#</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2</td>
<td>Strictures **</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>Penetrating††</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from *Inflamm Bowel Dis* 2000;6:8–15.

*The age when diagnosis of Crohn’s disease was first definitively established by radiology, endoscopy, pathology, or surgery.

†The maximum extent of disease involvement at any time before the first resection. Minimum involvement for a location is defined as any anastomosis or ulceration. Mucosal erythema and edema are insufficient. For classification, both small and large bowel examination are required.

‡Disease is limited to the terminal ileum (the lower third of the small bowel) with or without spillover into the cecum.

§Any colonic location between cecum and rectum with no small bowel or upper gastrointestinal involvement.

¶Disease of the terminal ileum with or without spillover into the cecum and any location between the ascending colon and rectum.

‖Any disease location proximal to the terminal ileum (excluding the mouth) regardless of additional involvement of the terminal ileum or colon.

#Inflammatory disease that has never been complicated at any time in the course of the disease.

**Strictures** is defined as the occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic, or surgical-pathologic methods with prestenotic dilatation or obstructive signs/symptoms without the presence of penetrating disease at any time in the course of the disease.

††Penetrating disease is defined as the occurrence of intrabdominal or perianal fistulas, inflammatory masses and/or abscesses at any time in the course of the disease. Perianal ulcers are also included. Excluded are postoperative intra-abdominal complications and perianal skin tags.
Silverstein and colleagues examined the lifetime clinical course of Crohn’s disease in a 24-year, population-based inception cohort of patients and also found that most of the clinical course is spent in remission, either medical or surgical. The authors found that Crohn’s disease is quiescent through much of its clinical course, as shown by the fact that the majority (65%) of follow-up time is spent in states characterized by medical or surgical remission. In fact, Faubion and associates found that only 43% of patients with Crohn’s disease in Olmstead County, Minnesota, ever required corticosteroids, which was similar to the rate of 56% found by Munkholm in Copenhagen County, Denmark. These population-based studies indicate that the overall clinical course of Crohn’s disease in the community is relatively mild, and many patients with Crohn’s disease are either in a mild disease state or in remission. Therefore, Crohn’s patients may never require aggressive treatment with more toxic agents.

TREATMENTS

Management strategies for Crohn’s disease are targeted at reducing disease symptoms while maintaining or improving a patient’s quality of life. A sequential approach of first inducing and then maintaining remission is standard practice in the treatment of Crohn’s disease. The current therapeutic approaches for Crohn’s disease depend on defining the disease location and severity, and should be individualized according to a patient’s response and tolerance to medical intervention. It is imperative to keep in mind that the most important therapeutic goal in Crohn’s disease is the maintenance of remission; this is the disease state that many Crohn’s patients will spend the majority of their lives in. There are many drugs that can be successfully used for inducing remission of an acute phase, but maintenance with the same drugs often fails or is discontinued because of side effects. Thus the choice of an initial therapeutic agent for treating Crohn’s disease must be made with the long-term aspects of the disease in mind: Crohn’s is not a short-term disease and once remission is achieved, it must be maintained, and the choice of maintenance therapy will depend on what agent or agents were used to induce remission. Patient education also plays a crucial role in the management of Crohn’s disease, and patients should therefore be educated about the toxicities of the different medications and what they can expect from their medical therapy.

Figure 1 shows the “treatment pyramid” that groups the therapeutic agents in a “step-up” manner according to their use in different Crohn’s disease severity levels. Generally, a step-up approach of adding therapies as a patient moves from mild to severe disease is used in clinical practice. Treatments currently used for mild to moderate Crohn’s disease include aminosalicylates, antibiotics, and the controlled-release corticosteroid budesonide. Treatments for moderate to severe Crohn’s disease include corticosteroids, infliximab, and immunomodulators.

Aminosalicylates

The aminosalicylates remain the cornerstone first-line therapy for the treatment of mild to moderate Crohn’s disease. Sulfasalazine and 5-aminosalicylic acid (mesalamine) are the most commonly used aminosalicylates; sulfasalazine consists of a sulfonamide antibiotic (sulfapyridine) linked by an azo bond to an anti-inflammatory salicylate (mesalamine). The National Cooperative Crohn’s Disease Study found sulfasalazine (1 g/15 kg body weight, with a maximal dose of 5 g/d) to be superior to placebo in patients with colonic disease (ileocolitis or colitis), but not in patients with small bowel disease. The European Cooperative Crohn’s Disease Study also found sulfasalazine (3 g/d) to be an effective treatment of patients with colonic disease. Later studies with controlled-release (Pentasa) and delayed-release (Asacol, Salofalk) mesalamine formulations in patients with different disease locations demonstrated that, with adequate doses, mesalamine is an effective treatment of Crohn’s disease: Tremaine and associates found 3.2 g/d Asacol to be an effective treatment of patients with active Crohn’s colitis or ileocolitis, while Singleton and colleagues found 4 g/d Pentasa to be an effective treatment of active Crohn’s ileitis, ileocolitis, and colitis. Thus, an important distinction between the Asacol and Pentasa mesalamine formulations is their effectiveness in treating different Crohn’s disease locations; while Asacol is an effective treatment of colitis or ileocolitis, Pentasa is an effective treatment of both small and large bowel disease. In addition, Prantera and associates found 4 g/d Asacol to be equally as effective as 40 mg/d methylprednisolone in the treatment of ileitis, and Gross and colleagues found 4.5 g/d Salofalk to have efficacy comparable to methylprednisolone (initially 48 mg/d, with subsequent weekly tapering) in the treatment of ileocolitis. Although studies by Mahida and associates and Rasmussen and colleagues found mesalamine to be no more effective than placebo, these studies used an insufficient dose (1.5 g/d) of mesalamine that is now known to be ineffective. A meta-analysis of the efficacy of Pentasa in the treatment of active Crohn’s disease also found an overall positive treatment effect.
Side effects are seen more frequently with sulfasalazine than with mesalamine; sulfasalazine has been associated with significant intolerance, resulting in the withdrawal by nearly one third of patients. Side effects associated with sulfasalazine treatment include anorexia, nausea, vomiting, abdominal cramps, headaches, general malaise, and dizziness. Fewer side effects have been seen with the mesalamine formulations; adverse events reported in clinical trials with mesalamine have been generally mild and reversible, with very few toxicities. Adverse events associated with the mesalamine formulations; side effects have been seen with the mesalamine formulations; adverse events reported in clinical trials with mesalamine have been generally mild and reversible, with very few toxicities. The available mesalamine delivery limiting its absorption. The available mesalamine delivery systems include pH-dependent, colonic flora-dependent, and moisture-activated (controlled-release) oral formulations (see Table 2). The pH-dependent formulations (Salofalk, Claversal, Mesasal, and Asacol) are encased in acrylic resins that are resistant to low intestinal pH, but dissolve once exposed to the higher pHs found in the more distal regions of the gastrointestinal tract. The formulations that are colonic flora-dependent contain mesalamine bonded to either sulfapyridine, itself (Dipentum), or an inert carrier (Colazide). The bonds are cleaved by the azoreductase, an enzyme produced by bacteria in the colon, and these formulations are therefore dependent upon both reliable bacteria levels as well as adequate residence time in the colon to ensure the release of mesalamine. The Pentasa formulation is moisture activated, consisting of microgranules of mesalamine coated with an ethylcellulose membrane. This allows for the release of mesalamine from the microgranules upon exposure to moisture and continuous delivery through the small and large bowel. The development of mesalamine formulations with different sites of delivery in the gastrointestinal tract has made the proper identification of disease location crucial to optimizing therapy in Crohn’s disease.

**Antibiotics**

Bacteria are one of the putative etiological factors of Crohn’s disease, although their precise role is unclear. Antibiotics have, therefore, been tested as a treatment of Crohn’s disease. Metronidazole is the most widely used antibiotic in the treatment of Crohn’s disease, and has been found to be superior to placebo in a 16-week trial. Metronidazole (0.8 g/d) has also been found to be comparable to sulfasalazine (3 g/d) in a 16-week, crossover Scandinavian trial. Common side effects associated with metronidazole include nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, and abdominal cramping. A serious side effect associated with long-term metronidazole treatment is peripheral neuropathy, which can occur in up to 50% of patients. There are also concerns about metronidazole’s potential mutagenic, carcinogenic, and teratogenic effects.

Ciprofloxacin is a fluoroquinolone antibiotic that has been found to be equally effective, at a 1-g/d dose, as 4 g/d mesalamine in the treatment of mild to moderate Crohn’s disease. However, tendonitis and tendon rupture, most often affecting the Achilles tendon, has been reported with fluoroquinolones. Van der Linden and colleagues found a relative risk of 3.2 (95% CI, 2.1 to 4.9) for developing Achilles tendon disorders in patients aged 60 and over with current fluoroquinolone use. The relative risk rises to 6.2 (95% CI, 3.0 to 12.8) in patients aged 60 or over when corticosteroids are used concurrently with fluoroquinolones. There are reports that metronidazole in combination with ciprofloxacin is an effective treatment of Crohn’s disease. However, there are potentially severe complications when these drugs are used, including the possible development of resistant bacteria during long-term use. Because of these concerns, antibiotics may be most effectively used as an adjuvant therapy, possibly in combination with mesalamine.

**Budesonide**

Corticosteroids are highly effective in achieving clinical remission in Crohn’s disease, but the benefits associated with corticosteroids are frequently offset by their serious toxic side effects. Some of the side effects of corticosteroids include cushingoid features, psychologic effects, ocular effects, peptic disease, hypertension, diabetes, dermatological problems, myopathy, and osteoporosis. Although osteoporosis can develop in inflammatory bowel disease patients without steroids, treatment with corticosteroids significantly contributes to bone

**TABLE 2. Properties of Mesalamine Preparations**

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Mechanism of Release</th>
<th>Site of Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentasa (mesalamine)</td>
<td>Individual microgranules of mesalamine coated with ethylcellulose membrane</td>
<td>Diffusion-dependent prolonged release through a semipermeable membrane</td>
<td>Duodenum, jejunum, ileum, colon</td>
</tr>
<tr>
<td>Asacol (mesalamine)</td>
<td>Mesalamine coated with Eudragit S</td>
<td>pH-dependent delayed release (≥7)</td>
<td>Distal ileum, colon</td>
</tr>
<tr>
<td>Salofalk Claversal Mesasal</td>
<td>Mesalamine coated with Eudragit L</td>
<td>pH-dependent delayed release (≥6)</td>
<td>Jejunum, ileum, colon</td>
</tr>
<tr>
<td>Colazide (balsalazine)</td>
<td>Mesalamine conjugated to inert carrier molecule</td>
<td>Colonic bacteria azoreduction</td>
<td>Colon</td>
</tr>
<tr>
<td>Dipentum (olsalazine)</td>
<td>Mesalamine dimer</td>
<td>Colonic bacteria azoreduction</td>
<td>Colon</td>
</tr>
</tbody>
</table>

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loss, and the bone loss is especially rapid shortly after administration (a few weeks to months) of steroids. Over 35% of patients treated acutely with corticosteroids will also become steroid dependent or steroid resistant. In addition, corticosteroids are ineffective at maintaining remission in Crohn’s disease patients.

For some patients, the side effects of corticosteroids can be avoided by the use of budesonide. Budesonide is a corticosteroid with extensive first-pass liver metabolism, resulting in low systemic bioavailability. A dose-ranging, placebo-controlled trial found that budesonide was more effective than placebo for inducing remission in patients with mild to moderate Crohn’s disease of the terminal ileum and proximal colon. The optimal dose identified from the study was 9 mg/d. However, budesonide is not without steroid-associated side effects; Campieri and associates found that while 9 mg/d budesonide was as effective as 40 mg/d prednisolone in the treatment of active Crohn’s disease, the proportion of patients suffering from steroid-associated side effects was similar. Although Rutgeerts and colleagues found that a lower percentage of patients treated in the budesonide treatment group (33%) suffered from steroid-associated side effects than in the prednisolone treatment group (55%), the authors also found a lower percentage of patients on budesonide than prednisolone achieved remission. This difference, however, did not reach statistical significance.

Budesonide has a limited treatment population; it is not effective in 30% to 40% of patients, and patients with more extensive colitis or left-sided colitis will not benefit from budesonide treatment. All controlled studies performed on budesonide to date have been restricted to patients with no fistulae present during the study, so budesonide’s role in patients with fistulizing Crohn’s disease remains uncertain. In addition, although budesonide may allow for the tapering of conventional steroids without short-term relapse, it is ineffective in preventing relapse beyond the first few months, which severely limits its utility as maintenance therapy.

Maintenance Therapy

Again, the most important therapeutic goal in Crohn’s disease is the maintenance of remission. The choice of a maintenance agent will depend on the initial therapeutic agent or agents used to achieve remission. If aminosalicylates have been used to induce remission, they can be continued as maintenance agents. It has also been shown that mesalamine may be an effective maintenance agent after surgery. If antibiotics have been used as the initial therapeutic agent, mesalamine can be used as a maintenance agent. Antibiotics can also be continued as maintenance agents, but concerns about their side effects as well as the potential to develop resistant bacteria present serious drawbacks to their long-term use. If corticosteroids have been used, maintenance therapy becomes more problematic. The side effects of systemic corticosteroids prevent their long-term use, and conventional steroids as well as budesonide are not effective at maintaining remission. Mesalamine is not an effective maintenance agent once steroid therapy has been used, and although there is some evidence that mesalamine facilitates steroid withdrawal, it only reduces the relapse rate in certain patient groups after steroid therapy. In addition, although the short-term safety of budesonide has been well defined, its safety during long-term use has not been established. It remains unclear whether budesonide will also result in the same long-term side effects, such as osteoporosis, adrenal gland suppression, or dependency, seen with conventional corticosteroids.

The primary agents for maintenance therapy after steroids have been immunomodulators. The immunomodulators 6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA) have been effective in allowing reduction in steroid doses and maintaining remission after steroid-inductive therapy. A drawback with AZA/6-MP is the relatively slow onset of action, requiring 3 to 6 months to demonstrate a beneficial clinical effect, and rare but serious side effects, including bone marrow suppression and pancreatitis. It is also important to keep in mind the potential drug–drug interaction between AZA/6-MP and mesalamine. Mesalamine is a competitive inhibitor of thiopurine methyltransferase (TPMT), an enzyme involved in the metabolism of 6-MP, and this inhibition results in increased metabolism of 6-MP to 6-thioguanine nucleotide (6-TG). The 6-TG metabolite has been associated with the clinical efficacy of AZA/6-MP. The addition of mesalamine therefore could allow patients to take lower doses of AZA/6-MP, but this has yet to be proven in prospective, randomized, and controlled clinical trials. However, low levels of TPMT have also been associated with bone marrow suppression, so caution must be used when combining mesalamine and AZA/6-MP therapies.

Methotrexate (MTX) has been found to be an effective maintenance therapy for patients with Crohn’s disease. MTX has been found to be well tolerated, but there are still concerns about the potential risk of liver disease from MTX treatment. Other rare but serious side effects associated with MTX treatment include reversible bone marrow depression and pneumonitis. There are also concerns about the potential teratogenicity of MTX.

TREATMENT ALGORITHMS FOR MILD TO MODERATE CROHN’S DISEASE

A patient’s response to the initial therapy should be evaluated within several weeks. If the patient is responding, the patient should continue the treatment until symptomatic remission is achieved or the treatment fails to result in improvement. Patients who achieve remission should be considered for maintenance therapy. Patients whose symptoms persist should be treated with another agent after initial therapy has been optimized and adherence to therapy has been established.
As is shown in Figure 2, our current practice patterns (illustrated in the algorithms) for the treatment of mild to moderate Crohn’s disease depend on the initial therapeutic agent used.

When mesalamine is used as the initial therapeutic agent, it should be continued as long as the patient shows a response. If the patient does not respond to mesalamine, budesonide can be added if the disease is confined to the ileum and/or the right colon. Antibiotics can also be considered for patients with colonic disease.

If antibiotics have been used as first agent to treat active disease, mesalamine should be used as a maintenance agent because of the potential serious side effects associated with long-term use of antibiotics. If the patient fails to respond to antibiotics, mesalamine or, for patients with ileal and/or right colonic disease, budesonide should be considered.

When budesonide is used as the initial therapeutic agent and the patient responds, the budesonide dosage must then be tapered. If a patient continues to respond after tapering, another therapeutic agent such as mesalamine must be used since budesonide is ineffective at maintaining remission. If a patient does not respond after tapering, an immunomodulator should be considered. If a patient does not respond to the initial budesonide treatment, mesalamine or antibiotics can be used.

If a patient does not respond to mesalamine, antibiotics, and budesonide or has moderate disease, oral prednisone and an elemental diet, or infliximab alone or in combination with immune modulators, are reasonable next steps.

INVERTING THE TREATMENT PYRAMID

Recent developments in therapies for Crohn’s disease have resulted in the reassessment of management strategies currently employed for the treatment of the disease. Specifically, the question of whether it is possible to alter the natural history of Crohn’s disease by introducing therapies currently reserved for the “top” of the treatment pyramid has been the subject of much discussion. Is it possible, by using agents early on that promote mucosal healing, to prevent the occurrence of chronic complications, such as fibrosis, stricture, and possibly fistulae? Although this has yet to be proven with any agent, there are some indications that corticosteroids and infliximab can promote mucosal healing. However, as discussed previously, corticosteroids can be associated with serious side effects, and infliximab can also be associated with drawbacks, such as acute and delayed infusion reactions, reactivation of latent tuberculosis, and the development of anti-DNA and anti-infliximab antibodies. In addition, infliximab is an expensive treatment, with the average third-party reimbursement per dose administered to a 70-kg patient of more than $5,200.12 Also, it is important to keep in mind that the Crohn’s disease course in the majority of patients is relatively mild: less than half of patients with Crohn’s disease will ever require corticosteroids during their lifetime.7 Thus, an aggressive approach of using more toxic treatments early on during treatment may not be necessary for the majority of Crohn’s disease patients, who could instead be effectively treated with milder and less toxic agents such as aminosalicylates.

The development of an improved classification system that would allow for the identification of particular subgroups with differing disease phenotypes and prognoses could play a factor in deciding between a step-up or top-down approach. However, clinical trials that would allow for the evaluation of short- and long-term safety, efficacy, and costs of step-up versus top-down therapeutic approaches are needed before the standard step-up approach is altered.

PATIENT ADHERENCE AND OUTCOMES IN CROHN’S DISEASE

Medication Adherence in Inflammatory Bowel Disease

The success of any treatment of inflammatory bowel disease is in large part dependent upon patient adherence to a
treatment regimen. However, a recent study found that only 40% of patients with ulcerative colitis on maintenance mesalamine took at least 80% of their medication, even though adherent behavior is a strong risk factor for disease recurrence: a study by Kane and colleagues examining the effects of nonadherence with mesalamine among patients with quiescent ulcerative colitis found that adherent patients had an 89% chance of maintaining remission, compared with only 39% in the nonadherent group. These studies emphasize the importance of enhancing treatment adherence in improving treatment outcomes in inflammatory bowel disease.

The chronic nature of Crohn’s disease presents a challenge for patient adherence. Patients often tire of taking medications once remission has been achieved, which can result in relapse and the need to revert to an inductive therapy. It is therefore crucial to educate patients about the importance of continued adherence to prevent relapse of disease or complications during the transition from inductive to maintenance therapy. Other patient-related reasons for nonadherence include: 1) not having the skills or knowledge necessary to complete an assignment, 2) not believing that the benefits of a treatment outweigh its costs, and 3) being in an environment that is not supportive of or interferes with adherence.

Behavioral Interventions to Improve Outcomes

Patient education is one method of improving patient adherence. A study by Martin and associates found that 62% of patients with ulcerative colitis and 78% of patients with Crohn’s disease consider themselves to be insufficiently informed about their disease. The same study also found that Crohn’s disease patients were particularly interested in learning about new treatments, etiology, symptoms, diet, and treatment and cancer risks associated with their disease. Open lines of communication aid in strengthening the relationship between the physician or healthcare provider and patient, which in turns helps to improve patient adherence. Simplifying the medical regimen can also enhance patient adherence; a study by Shale and colleagues on compliance with delayed-release mesalamine in patients with inflammatory bowel disease found that the most significant risk factor for partial noncompliance was a 3-times-daily dosing regimen. A recent study also found that concentrations of delayed-release mesalamine are similar whether the drug is administered in 3 divided doses or as a single daily dose. The results of these 2 studies suggest that once- or twice-daily dosing is a viable and desirable dosing regimen that could improve patient adherence. Finally, a collaborative management approach among all members of the healthcare team works to increase each member’s understanding of the patient’s needs. This understanding in turn facilitates the development of a customized treatment approach that takes into consideration a patient’s disease and therapeutic history, prior response and adherence to medica-

Cancer Risk in IBD Patients

Inflammatory bowel diseases have been associated with an increased risk of colon cancer that greatly increases with the extent and duration of the disease. An increased risk for adenocarcinoma of the small bowel has also been found in Crohn’s disease, although it remains a relatively rare occurrence. However, evidence is emerging that aminosalicylates may reduce the risk of colorectal cancer. Pinczowski and associates performed a case-control study of 102 patients with colorectal cancer in ulcerative colitis and matched controls without cancer, and found patients who completed at least 1 course of sulfasalazine therapy had a relative risk of 0.34 (95% CI, 0.19-0.62) of developing colorectal cancer compared with those who did not. Eaden and colleagues examined the role of mesalamine as a chemopreventative agent in 102 cases of colorectal cancer in ulcerative colitis with matched controls, and found that regular consumption of mesalamine and frequent visits to a physician reduced the cancer risk by 81% and 84%, respectively. These studies further underscore the importance of patient adherence to treatment in inflammatory bowel disease, especially with aminosalicylates, which may not only prevent relapses of the disease but may also reduce a patient’s risk of developing cancer.

CONCLUSION

Studies performed in tertiary care clinics indicating that the natural course of Crohn’s disease is toward the development of stricturing or penetrating disease must be balanced with population-based studies finding that the natural disease course is mild, with the majority of patients in remission or experiencing mild disease activity. The choice of first-line therapies is thus a crucial one, since most patients never require treatments beyond first-line agents. It is also important to keep in mind that Crohn’s is a lifelong disease, and the use of more aggressive therapies early on limits therapies that can be used in the future. Discussion of inverting the treatment pyramid is therefore premature.

The development of a classification system that could correlate an individual genotype or disease phenotype with a particular disease course could ultimately settle the debate over inverting the treatment pyramid in Crohn’s disease; such a classification could identify predictive factors for the Crohn’s disease evolution in an individual patient, thereby facilitating the selection of the most appropriate therapeutic agents for that patient. However, at this point, we are still lacking such a classification system. Future studies on the genetic and environmental factors influencing a patient’s Crohn’s disease course will hopefully allow for the development of such a system.
In developing management strategies for patients with Crohn’s disease, it is imperative to consider both the short- and long-term aspects of the disease. The most important therapeutic goal for Crohn’s disease is the maintenance of remission, since this is the state in which many Crohn’s disease patients will spend the majority of their lives in. Identifying the disease location plays an integral role in optimizing a treatment regimen since the disease location is a major determinant of the clinical course and prognosis of the disease. The advent of medications with topical activity targeted to specific bowel regions has also made establishing the disease location essential to determining appropriate therapy. The aminosalicylates therefore remain the foundational therapy for mild to moderate Crohn’s disease because of their effectiveness, favorable side effect profile, and availability of formulations that can be used to treat small and/or large bowel disease. Antibiotics can also be used to treat mild to moderate Crohn’s, although there are potentially serious side effects associated with their long-term use. Budesonide can also be used as a first-line agent, although it is only effective for ileal and right ileocolonic disease. In addition, budesonide is an ineffective maintenance agent. Management strategies for Crohn’s disease should ultimately be tailored toward a patient’s particular disease location and history, using the least toxic agent.

REFERENCES