DRUG THERAPY

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INFLAMMATORY BOWEL DISEASE

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IN recent years there has been a series of advances in the treatment of inflammatory bowel disease (ulcerative colitis and Crohn's disease).[1-6] Notwithstanding these advances, our understanding of inflammatory bowel disease[7] has been hindered by the lack of representative animal models, an absence of pathognomonic features, and inadequate therapeutic end points. Sensitive or specific serologic or genetic markers of inflammatory bowel disease have yet to be identified.[7] At present, the diagnosis of ulcerative colitis and Crohn's disease and the differentiation between them are based on nonspecific clinical and histologic patterns that are often obscured by intercurrent infectious or iatrogenic events[8] or altered by medication[9] or surgery.

MEASUREMENT OF DISEASE ACTIVITY

The assessment of therapy in patients with inflammatory bowel disease is hampered by the absence of well-defined end points of disease activity.[10,11] The critical factors for determining therapeutic options are the location, extent, and severity of the disease and its response to current or previous treatment. The extent of ulcerative colitis and the location of disease in patients with Crohn's disease have become relevant because of the availability of rectal, delayed-release, and controlled-release medications with topical (mucosal) activity that have maximal antiinflammatory effects in the intestine with minimal systemic activity or toxic effects.

Ulcerative Colitis

In patients with ulcerative colitis, the activity of the disease is assessed primarily on the basis of clinical features,[10,11] most often with the criteria of Truelove and Witts (Table 1).[12] These criteria are clinically useful, although many patients have features that fall between those classified as mild and those classified as severe. Disease activity can also be assessed endoscopically.[10,13,14] The histologic findings loosely parallel the endoscopic features.[15]

The primary end points of therapy should be the induction and maintenance of remission.[11] The definition of remission must account for the ability of the mucosa to heal, the variability of normal bowel patterns, and associated irritable-bowel symptoms.[16] The gastrointestinal advisory panel of the Food and Drug Administration has proposed that remission be defined as an "absence of inflammatory symptoms (rectal bleeding or diarrhea) in conjunction with evidence of mucosal healing (absence of ulceration, significant granularity or friability)."[17] Maintenance therapy should prevent a recurrence of clinical or endoscopic signs of active disease. Less stringent evidence of improvement (e.g., a reduction in bowel movements, diarrheal stools, bleeding, or abdominal cramps, supported by endoscopic or histologic evidence of less severe activity) is more difficult to interpret.[10,11]

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Crohn's Disease

Assessing disease activity in patients with Crohn's disease is more difficult, because the clinical patterns and complications are more heterogeneous.[10,11,14] Comparing predefined subgroups of patients is impractical in most clinical trials, because the number of strata would be so large that there would be few patients in each stratum.[11] Evaluation of disease activity on the basis of individual therapeutic goals (e.g., healing of a fistula, a reduction in diarrhea, or the relief of abdominal pain),[11,14,18] although clinically useful, requires subjective interpretations by patient and physician. At present, disease activity is best quantified in clinical trials by using indexes of symptoms, signs, and inflammatory sequelae. The Crohn's Disease Activity Index, which consists of clinical variables correlated (by multiple regression analysis) with the physician's assessment of the patient's well-being (Table 2), has been repeatedly validated.[10,14,19] The index is not useful in clinical practice, however, and has been criticized because of its subjectivity (e.g., assessing well-being rather than disease) and interobserver variability.[10] Other methods of evaluating the severity of disease on the basis of clinical findings, the results of laboratory tests, endoscopic features, or quality of life have been developed, but none of these methods have superseded the Crohn's Disease Activity Index in clinical trials or for regulatory purposes.[15-25]

It is more difficult to define remission in Crohn's disease than in ulcerative colitis,[11] because the correlation between clinical activity (or the score on the Crohn's Disease Activity Index) and endoscopic findings is poor.[15,26] Hence, most investigators define clinical remission as an index score of less than 150.[10]

MEDICAL THERAPY

Corticosteroids

Corticosteroids were the first medications to be evaluated systematically in patients with inflammatory bowel disease.[27] In addition to their nonspecific effects on cellular and humoral immune function, corticosteroids inhibit the production and action of cytokines and inflammatory mediators,[28-32] enhance sodium and water absorption, and improve the sense of well-being.[33]

When administered orally, parenterally, or rectally, corticosteroids (or corticotropin) are effective in patients with active ulcerative colitis or Crohn's disease.[27,30,31,34,35] Whether the systemic actions of cortico-

steroids are more beneficial than their local (mucosal) actions is uncertain, and the question has become particularly important because of the advent of rapidly metabolized preparations that can be applied topically or delivered orally to distal sites in the digestive tract.[36-38] Similarly, whether corticosteroids are more effective when given as divided oral doses or as intermittent or continuous intravenous infusions is not known.[38] In a trial involving patients with active ulcerative colitis, a daily dose of 40 or 60 mg of prednisone was superior to a daily dose of 20 mg.[39] Corticotropin continues to be favored by some clinicians.[40]

Rectal administration of hydrocortisone and prednisolone is useful in treating distal colonic disease, but prolonged therapy induces Cushing's syndrome and adrenal suppression.[28,31,41] Conjugation of prednisone or prednisolone with esters that minimize absorption (e.g., prednisolone metasulfobenzoate) and new steroid molecules with enhanced receptor-binding properties but more rapid presystemic metabolism (e.g., beclomethasone diproprionate, tixocortol pivalate, and budesonide)[28,35] maximize the mucosal effects while minimizing systemic exposure. Budesonide has been formulated as an enema[42] and is being investigated in oral controlled-release formulations delivered to the ileum or colon.[5,6] The results of recent trials were favorable, but questions remain about the risk of systemic exposure to formulations with 10 percent of the bioavailability of cortisone but more than 100 times the receptor-binding affinity.[5,6,37]

The toxic effects of corticosteroids are related to the dose and duration of therapy. Complications of treatment in patients with inflammatory bowel disease[28,31] include the masking (or induction) of intestinal perforation,[43,44] osteonecrosis,[45] and metabolic bone disease,[46] as well as growth retardation in children.[47] Arthralgia associated with the withdrawal of corticosteroids must be distinguished from the extraintestinal manifestations of inflammatory bowel disease.[28] Corticosteroids have been used successfully throughout pregnancy in women,[48] and alternate-day therapy may minimize growth impairment in children.[47]

Table 1. Criteria for Evaluating the Severity of Ulcerative Colitis.*

Variable	Mild Disease	Severe Disease	Fulminant Disease
Stools (no./day)	<4	>6	>10
Blood in stool	Intermittent	Frequent	Continuous
Temperature (°C)	Normal	>37.5	>37.5
Pulse (beats/min)	Normal	>90	>90
Hemoglobin	Normal	<75% of normal value	Transfusion required
Erythrocyte sedimentation rate (mm/hr)	≤30	>30	>30
Colonic features on radiography	—	Air, edematous wall, thumbprinting	Dilatation
Clinical signs	—	Abdominal tenderness	Abdominal distention and tenderness

*Based on the criteria of Truelove and Witts.[12] Moderate disease includes features of both mild and severe disease.

Table 2. Crohn's Disease Activity Index.*

Variable	Multiplication Factor
No. of liquid or soft stools (each day for seven days)	2
Abdominal pain (0, none; 1 or 2, intermediate; 3, severe)	5
General well-being (0, good; 1, 2, or 3, intermediate; 4, poor)	7
No. of complications Arthralgia or arthritis Iritis or uveitis Erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis Anal fissure, fistula, or abscess Other fistula Fever (>37.8°C) during previous week	20
Use of opiates for diarrhea (0, no; 1, yes)	30
Abdominal mass (0, none; 2, questionable; 5, definite)	10
47 minus hematocrit (men), 42 minus hematocrit (women)	6
Percentage deviation above or below standard weight	1

*The score on the index is calculated by multiplying the numerical value for each variable by the multiplication factor shown and totaling the resulting values. A score below 150 indicates remission; a score above 450 indicates severe illness. Based on the index of Best et al.[19]

Dependency on corticosteroids is often encountered in patients with inflammatory bowel disease.[49] In many cases, the dose of corticosteroids cannot be tapered without an increase in disease activity. However, the results of controlled trials offer little support for long-term treatment with low doses of corticosteroids to prevent a relapse of either ulcerative colitis or Crohn's disease.[50] Hence, corticosteroid therapy is indicated primarily for the short-term induction of a remission of inflammatory bowel disease and not as maintenance therapy (Tables 3 and 4).[51-53] Corticosteroid suppositories or enemas can be used as first-line therapy in patients with mild or moderately active ulcerative proctitis or left-sided colitis. In addition, rectal corticosteroids are useful as adjunctive therapy in patients with severe colitis who are receiving parenteral corticosteroids. Oral prednisone or prednisolone is indicated for moderate or severe ulcerative colitis or Crohn's disease but should be tapered once a clinical response has been achieved.

Parenteral corticosteroids are reserved for hospitalized patients with severe or fulminant disease; in 7 to 10 days, most patients will have a response to intravenous therapy with the equivalent of 40 to 60 mg of prednisone daily. When bowel movements have returned to normal and the patient is able to eat normally, oral prednisone (or prednisolone) is substituted and then tapered according to the clinical response. Patients in whom corticosteroids cannot be tapered and then discontinued, despite the administration of an ami-

Table 3. Therapeutic Options for Patients with Ulcerative Colitis.

Mild or moderate disease
Distal colitis
Aminosalicylate (oral or rectal)*
Rectal corticosteroid†
Extensive colitis
Oral aminosalicylate
Severe disease
Distal colitis
Oral corticosteroid
Rectal corticosteroid†
Extensive colitis
Oral corticosteroid
Fulminant disease
Extensive colitis
Parenteral corticosteroid
Intravenous cyclosporine‡
Remission
Distal colitis
Aminosalicylate (oral or rectal)*
Oral azathioprine or mercaptopurine§
Extensive colitis
Oral aminosalicylate
Oral azathioprine or mercaptopurine§

*A rectal aminosalicylate may be prescribed alone or in combination with an oral aminosalicylate.

†A rectal corticosteroid may be prescribed alone or in combination with an oral aminosalicylate or an oral corticosteroid.

‡Cyclosporine is reserved for the treatment of patients who do not have a response to intensive intravenous corticosteroid therapy.

§Azathioprine or mercaptopurine is used in treating corticosteroid-dependent patients and those with refractory disease.

nosalicylate or immune modifier (see below), should be considered candidates for surgery.

Aminosalicylates

Sulfasalazine and 5-aminosalicylic acid (mesalamine) analogues are most commonly used to treat mild or moderately active ulcerative colitis[35,51,52] and Crohn's disease[34,53] and to maintain remission.[50,54] Sulfasalazine, which consists of a sulfonamide antibiotic (sulfapyridine) linked by an azo-bond with an antiinflammatory salicylate (mesalamine), was developed for delivery to the synovial tissue in patients with arthritis. Studies in patients with arthritic symptoms and ulcerative colitis suggested that the drug ameliorated the colitis,[55] and these findings led to clinical trials that confirmed the usefulness of sulfasalazine in treating mild or moderately active ulcerative colitis[29] and maintaining remission.[52,54] Sulfasalazine is not as effective as corticosteroids for inducing remission in patients with moderate or severe disease.[51,52] Two trials compared sulfasalazine and corticosteroids in the treatment of Crohn's disease. In the National Cooperative Crohn's Disease Study, 604 patients received sulfasalazine (1 g per 15 kg of body weight per day, with a maximal dose of 5 g per day), prednisone (0.75 mg per kilogram per day), or placebo; sulfasalazine was found to be superior to placebo in patients with colonic disease (ileocolitis or colitis) but not in those with small-bowel disease.[56] In the European Cooperative Crohn's Disease Study, which compared sulfasalazine (3 g per day) with methylprednisolone (initially 48 mg per day with weekly tapering) in 452 patients,[43] sulfasalazine was also effective in patients with colonic disease, but prednisolone resulted in greater short-term improvement. Low-dose sulfasalazine was not effective in maintaining clinical remission in either study.

Subsequent studies showed that sulfasalazine is poorly absorbed in the upper digestive tract and is split in the colon by bacteria into sulfapyridine and mesalamine.[28,57,58] Sulfapyridine is absorbed from the colon, undergoes acetylation in the liver, and is excreted in urine. Mesalamine is poorly absorbed from the colon and is excreted in the feces after acetylation by colonic bacteria or within the colonic epithelium. The primary fecal metabolite, *N*-acetyl-5-aminosalicylic acid, is inactive because of limited epithelial uptake. We now know that the intestinal antiinflammatory activity of mesalamine is equivalent to that of sulfasalazine[59,60] and that sulfapyridine functions primarily to deliver mesalamine to the colon but accounts for most of the side effects of sulfasalazine.[28] These findings explain the different results in patients with colonic disease and those with small-bowel disease. In addition, since mesalamine is rapidly absorbed from the upper digestive tract[28,57,58] but has little systemic activity, its proximal absorption must be minimized so that it is delivered to distal sites of intestinal inflammation.

Formulations of mesalamine have been developed to maximize its release at sites of inflammation while limiting its absorption.[28,31,61-63] The drug has been stabilized with antioxidants for rectal administration. For oral administration, it has been formulated within acid-stable enteric delivery systems or conjugated with alternative carriers.[28,57,58,61,62] In the United States, mesalamine is marketed in the form of suppositories and enemas for rectal administration and in oral formulations either with a resin coating that breaks down at a pH of 7 (the approximate pH of the distal ileum and

Table 4. Therapeutic Options for Patients with Crohn's Disease.

Mild disease
Oral aminosalicylate*
Metronidazole†
Moderate disease
Oral corticosteroid
Azathioprine or mercaptopurine‡
Severe disease
Parenteral corticosteroid
Intravenous cyclosporine§
Remission
Oral mesalamine¶
Azathioprine or mercaptopurine‡

*Sulfasalazine is used for colonic disease.

†Alternative antibiotics (e.g., ciprofloxacin) are commonly used.

‡These drugs are prescribed for corticosteroid-dependent patients and for those with refractory disease or perianal fistulas.

§Intravenous cyclosporine therapy is effective in patients with refractory fistulas or severe disease. The long-term benefits, however, have not been proved.

¶Mesalamine is effective in patients who have a response to oral aminosalicylate therapy, and it prevents postoperative recurrence of disease.

proximal colon) or as a controlled-release preparation encapsulated in ethylcellulose microgranules.[64-66] Olsalazine, an aminosalicylic acid dimer, requires bacterial azo-reduction, like sulfasalazine, but releases two molecules of aminosalicylic acid into the colon.[63] Formulations available in other countries include rectal foams and oral preparations with resin coatings or azo-bonded carriers.[28,61] Commonly used doses and delivery formulations are listed in Table 5.

The antiinflammatory actions of aminosalicylates are not fully understood.[57,58] Sulfasalazine was developed to provide antibacterial and antiinflammatory properties.[55] Although it may have antibacterial properties not shared by mesalamine,[57,58] the focus on salicylate has led to studies of the arachidonic acid cascade and of cyclooxygenase and lipoxygenase metabolites.[7] After clinical trials had shown that cyclooxygenase inhibitors were not effective in the treatment of ulcerative colitis, interest shifted to the lipoxygenase pathway and the increased mucosal production of leukotriene B_4 in active colitis.[67] Although lipoxygenase inhibition reduces the development of acute colitis in animals,[57,67] potent lipoxygenase inhibitors were not effective in treating active ulcerative colitis and were less effective than aminosalicylates as maintenance therapy.[52] A possible explanation is that aminosalicylates can inhibit the production of cyclooxygenase, thromboxane synthetase, platelet-activating-factor synthetase,[68] and interleukin-1 by macrophages and can decrease immunoglobulin production by plasma cells.[57,58] Both sulfasalazine and mesalamine inhibit the production of reactive oxygen species and scavenge reactive oxygen metabolites.[69] Hence, most of the inflammatory cascades activated in inflammatory bowel disease are in some manner influenced by these agents.

Just as the efficacy of sulfasalazine is related to the dose, tolerance to the drug is dose-related and corresponds to genetically determined hepatic acetylation of sulfapyridine.[28,31,61] Common side effects, which include headache, nausea, and fatigue, respond to a reduction in the dose. Hypersensitivity reactions to the sulfa moiety include rash, fever, hepatitis, pneumonitis, hemolytic anemia, and bone marrow suppression. Up to 80 percent of men have reversible decreases in the number and motility of sperm, but reproductive function in women is unaffected.[28,31,61] Sulfasalazine impairs the absorption of folic acid, an effect that occasionally contributes to anemia and has led to the recommendation of folic acid supplementation.[28]

A primary advantage of the newer mesalamine derivatives over sulfasalazine is the improved tolerance.[28,31,61] Up to 30 percent of patients taking 4 g of sulfasalazine daily have side effects, whereas in clinical trials patients taking up to 4.8 g of mesalamine had no more side effects than those taking placebo. This benefit of mesalamine must be weighed, however, against the considerably lower cost of sulfasalazine. Rare hypersensitivity reactions, including pneumonitis, pancreatitis, hepatitis, nephritis, and worsening of colitis, have been reported with mesalamine.[28,31,61] Aminosalicylates have been used in women during pregnancy and breastfeeding and in children without untoward effects.[28,31,37,48]

Topical formulations of mesalamine are effective as first-line therapy for mild or moderately active disease and as maintenance therapy for distal ulcerative colitis (e.g., suppositories for proctitis and enemas for left-sided colitis).[64,65] Mesalamine enemas are also effective in treating distal colitis that is unresponsive to oral aminosalicylates or corticosteroids.[52,61,64] Oral aminosalicylates are effective in treating mild or moderately active ulcerative colitis[54] and Crohn's disease[66] and in maintaining remission in both diseases.[50] A dose–response relation is apparent with both active and maintenance therapy, although with maintenance treatment (at least for sulfasalazine), the usual dose is approximately 50

Table 5. Aminosalicylate Preparations.

Preparation	Dose	Formulation	Site of Delivery	Treatment Schedule*	
				Active therapy	Maintenance therapy
Topical or rectal					
Mesalamine enema	1–4 g	60- or 100-ml suspension	Left colon	1–4 g at bedtime	1 g at bedtime
Mesalamine suppository	500 mg or 1 g	—	Rectum	500 mg two or three times a day	500 mg at bedtime
Oral					
Azo-bond sulfasalazine	500 mg	Sulfapyridine carrier	Colon	4–6 g in divided doses	2–4 g in divided doses
Olsalazine	250 mg	5-aminosalicylate dimer	Colon	—†	1.5–3 g in divided doses
Balsalazide	750 mg	Aminobenzoylalanine carrier	Colon	2–6 g (?)	2–6 g (?)
Mesalamine derivatives					
Delayed-release Asacol	400 mg	Eudragit-S (pH 7)	Distal ileum, colon	2.4–4.8 g in divided doses	800 mg–4.8 g in divided doses
Delayed-release Claversal, Mesasal, or Salofalk	250 or 500 mg	Eudragit-L (pH 6)	Ileum, colon	1.5–3 g in divided doses	750 mg–1.5 g in divided doses
Sustained-release Pentasa	250 or 500 mg	Ethylcellulose microgranules	Stomach (?), colon	2–4 g in divided doses	1.5–3 g in divided doses

*There are insufficient data to assess dose–response relations in active or maintenance therapy for ulcerative colitis or Crohn's disease. Dose ranges are based on data reported by Margolin et al.,[27] Hanauer et al.,[28] Hawthorne and Hawkey,[30] Kornbluth et al.,[35] Sachar,[50] Sutherland et al.,[54] Allgayer,[61] Sutherland,[64] Marshall and Irvine,[65] and Singleton et al.[66]

†The usefulness of olsalazine as active therapy is questionable.

percent of the dose used for active treatment. In patients who do not have a response to active therapy or have a relapse while receiving maintenance treatment, a daily dose of up to 4 to 6 g of sulfasalazine or 4 to 5 g of mesalamine may be effective. Oral and rectal formulations can be used together (Table 3).[51,52]

Immunomodulatory Drugs

Azathioprine and Mercaptopurine

Immunomodulatory drugs are now accepted as appropriate for long-term treatment in some patients with Crohn's disease or ulcerative colitis.[30,31,70] Despite early evidence of the efficacy of azathioprine in treating inflammatory bowel disease, there was a reluctance to use the drug in young patients because of the associated risk of lymphoma. However, both azathioprine and mercaptopurine have proven long-term benefits in patients with either ulcerative colitis or Crohn's disease.[71,72] The addition of azathioprine or mercaptopurine to corticosteroids in patients with Crohn's disease allows tapering of the corticosteroids.[18,73] Likewise, azathioprine prolongs remission in corticosteroid-dependent patients with ulcerative colitis.[74]

Azathioprine is rapidly absorbed and converted to mercaptopurine in red cells. Subsequent hepatic conversion produces active metabolites that inhibit purine ribonucleotide and, hence, DNA synthesis.[28,30] Mercaptopurine itself is also rapidly absorbed. The mechanism of action of these drugs in inflammatory bowel disease may involve the inhibition of lymphocyte function, primarily that of T cells.[28,30] A decline in the activities of both natural killer cells and cytotoxic T cells is correlated with the clinical response, which requires three to six months of therapy.[18] An antiinflammatory effect may also be involved.[28,32] The usual doses are 2.0 to 2.5 mg of azathioprine per kilogram per day and 1.0 to 1.5 mg of mercaptopurine per kilogram per day.

Azathioprine and mercaptopurine are well tolerated.[28,75] A troublesome complication of both drugs is pancreatitis, which occurs in 3 to 15 percent of patients. It typically develops after several weeks of therapy, resolves spontaneously after the drug has been discontinued, and rapidly recurs if the drug is given again.[28,31,76] Both azathioprine and mercaptopurine cause bone marrow suppression, particularly neutropenia, which is dose-related, necessitating monitoring at least four times a year.[77,78] Concern about the carcinogenic and teratogenic potential of these drugs has been allayed by the results of a recent case–control trial involving patients with inflammatory bowel disease.[79] The drugs have been used safely in children, as well as in adults, and there is increasing evidence of their safety during pregnancy.[80]

Azathioprine or mercaptopurine is used as long-term therapy in patients with ulcerative colitis who become dependent on corticosteroids or do not have a response to aminosalicylate or corticosteroid therapy (Tables 3 and 4).[51,52] Similarly, patients with Crohn's disease in whom corticosteroids cannot be discontinued or who have persistent perianal disease or fistulas may benefit from long-term administration of azathioprine or mercaptopurine.[30,31,53,71]

Cyclosporine

The slow onset of action of azathioprine and mercaptopurine in patients with inflammatory bowel disease has led to trials of more potent immunosuppressive drugs, such as cyclosporine.[81] The primary indication for cyclosporine is acute, severe ulcerative colitis[2,82] or refractory Crohn's disease.[83,84] Continuous intravenous infusions have proved effective, whereas lower-dose oral regimens have not been consistently effective for either inducing or maintaining remission.[3,85] The primary side effect of cyclosporine is renal dysfunction, manifested as a decrease in glomerular filtration, interstitial nephritis, or both.[28,31] Other complications include neurotoxic effects and seizures (especially in patients with low serum cholesterol concentrations), immunosuppression, and opportunistic infections.[81] Currently, cyclosporine is reserved for the treatment of severe, refractory disease when surgery is not appropriate or before other therapies have taken effect (Tables 3 and 4).[81]

Methotrexate

A recent North American trial demonstrated significant corticosteroid-sparing effects of weekly injections of methotrexate (25 mg per week).[4] Additional studies are under way to determine whether lower doses are adequate for maintenance therapy. Because of the potential for bone marrow suppression and hepatic toxicity, blood counts and liver-enzyme concentrations must be monitored.[28,86] Whether the risk of hepatic fibrosis is increased in patients with inflammatory bowel disease is uncertain. Pulmonary toxicity is a rare hypersensitivity reaction. Folic acid provides protection against the effects of toxic methotrexate.[87]

Antibiotics

Although the enteric microflora provide an obvious target for therapy in patients with inflammatory bowel disease,[88] no combination of antibiotics has been found to alter the long-term course of the disease. The modest antibacterial properties of sulfasalazine[57] led to trials of other antibiotics in ulcerative colitis, but the results were disappointing.[89] Preliminary reports of a benefit from tobramycin or metronidazole administered as maintenance therapy for ulcerative colitis have not been confirmed.[52] Thus, antibiotic therapy for ulcerative colitis has been used on an empirical basis as a component of the intensive regimen of intravenous corticosteroids for patients with severe colitis.[90,91] Antibiotics have evolved as primary therapy for pouchitis after colectomy and ileoanal anastomosis for ulcerative colitis.[92]

There is more evidence supporting a role for antibiotics in Crohn's disease. Metronidazole is effective in treating perianal disease in patients with Crohn's disease[93] and is as effective as sulfasalazine[94] and superior to placebo[95] as single therapy for patients with

mild or moderately active disease. In addition, the administration of metronidazole immediately after bowel resection may delay anastomotic recurrence.[96] Since a relapse is likely after metronidazole has been discontinued, long-term therapy is required.[93] Prolonged treatment, however, carries the risk of peripheral neuropathy, especially in patients receiving more than 10 mg per kilogram per day.[31] There are limited data supporting the empirical use of other antibiotics in patients with Crohn's disease, although they are often given in an attempt to minimize the exposure to corticosteroids.[97,98] Recently, ciprofloxacin has gained favor, despite the absence of data from controlled trials.

Nutritional Therapies

Nutritional therapy for patients with inflammatory bowel disease has evolved with advances in the technology of enteral and parenteral nutritional support.[99,100] The bases for dietary or nutritional therapies are the possibility that a dietary factor contributes to the initiation or perpetuation of mucosal inflammation[7] and the demonstrated efficacy of nutritional support to patients with malnutrition, persistent malabsorption, and enteric protein loss. Although efforts to identify exacerbating dietary factors have failed, nutritional therapies may ameliorate inflammation while improving nutritional status.

Dietary intervention in patients with ulcerative colitis is aimed at reducing symptoms and providing adequate nutrition to compensate for reduced intake and increased colonic losses.[55,99,100] Neither an elemental diet nor total parenteral nutrition decreases the inflammation associated with ulcerative colitis. The recognition that colonic epithelium derives a substantial proportion of its energy from luminal short-chain fatty acids has led to trials of mixed short-chain-fatty-acid or butyrate enemas, with variable results.[101] Another approach is the use of omega−3 fatty acids to divert arachidonic acid metabolites away from leukotriene B_4 to less inflammatory derivatives of the leukotriene C or D classes. Large doses of fish oil do reduce inflammation and allow a reduction in the dose of corticosteroids in patients with ulcerative colitis,[102,103] but patients dislike the large doses and fishy breath.

In contrast to the results in patients with ulcerative colitis, elemental diets and total parenteral nutrition with bowel rest improve the symptoms, inflammatory sequelae, and nutritional status in patients with Crohn's disease.[99,100] The benefits are similar to those of corticosteroid therapy but are short-lived. In North America these approaches are used as a substitute for corticosteroid therapy primarily in children or adolescents who need the nutritional intake to grow and mature sexually.[47] Whether liquid polymeric diets, which are less expensive and can be made more palatable, can be substituted for elemental diets continues to be debated.[104] The rationale for elemental feedings includes the provision of excess glutamine, an energy source for small-bowel epithelium; reduced production of eicosanoid from fatty acids; and reduced antigenic or adjuvant responses to luminal bacteria and lipid fragments.[99,100] Total parenteral nutrition is not superior to elemental diets in treating Crohn's disease and is indicated only for severely malnourished patients or those unable to tolerate elemental feedings.

Supportive Therapy

Many therapeutic options are directed at the physiologic sequelae of inflammation or surgical resection.[31,51,53] The irritable bowel syndrome often occurs with inflammatory bowel disease.[16] Diarrhea and abdominal cramping can be treated with antidiarrheal or antispasmodic drugs, as long as the symptoms are mild and not accompanied by fever, abdominal tenderness, or evidence of obstruction or colonic dilatation. Likewise, patients with constipation may benefit from a bulk-type laxative. Resection of less than 100 cm of ileum often results in bile-salt malabsorption and diarrhea, which respond to low doses of cholestyramine. Patients receiving prolonged corticosteroid therapy should also receive calcium and vitamin D supplementation. Vitamin B_{12}, A, or D supplements may be required after ileal resection, and folic acid is recommended for patients receiving sulfasalazine.[52,53]

Narcotics should be avoided because of the potential for abuse in patients with chronic disease,[105] as well as the potential for inducing toxic megacolon. Nonsteroidal antiinflammatory drugs may exacerbate inflammatory bowel disease, because prostaglandin inhibition may increase the mucosal inflammation.[106]

Since there are no predisposing psychological factors in patients with inflammatory bowel disease, routine use of addictive anxiolytic or sedative drugs should be avoided.[107] Occasionally, patients may benefit from antidepressant drugs for secondary depression or chronic pain.

Future Therapy

Alternative aminosalicylate formulations, such as 4-aminosalicylic acid,[58] and delivery systems (e.g., balsalazide and mesalamine foams), continue to be developed.[58,61] The mechanisms of action of aminosalicylate that are under investigation include alterations in the profile of arachidonic acid derivatives, interactions with lymphocytes and immunoglobulin formation, intermediary metabolism of colonocytes (including the use of short-chain fatty acids), and antioxidant properties.

Future modifications of corticosteroids (e.g., budesonide) may increase their mucosal effects while minimizing the systemic impact.[36,37] Alternative site-specific delivery systems are also being evaluated. The response of patients with ulcerative colitis or Crohn's disease to immune-modifying drugs has led to a search for alternative immunosuppressive approaches. These include lymphocyte apheresis,[108] the inhibition of specific lymphocyte populations (e.g., monoclonal antibodies against CD4 lymphocytes)[109] and proinflammatory cytokines (e.g., tumor necrosis factor α),[110] and the use of antiinflammatory cytokines (interleukin-10 or interleukin-11) or mediators (interleukin-1–receptor antago-

nists).[72,111] Additional immune modifiers that may have a role in the treatment of inflammatory bowel disease include interferon regulatory proteins and intravenous immunoglobulin.[111]

Conclusions

The progressive, chronic course and sequelae of inflammatory bowel disease call for a long-term perspective on treatment and an approach that maximizes the mucosal antiinflammatory effects while minimizing the systemic impact. There has been a trend away from prolonged corticosteroid therapy because of the recognized long-term benefit of immune modulation with azathioprine or mercaptopurine. Exactly when patients should be treated with immune modifiers is a matter of controversy. The prevention or cure of ulcerative colitis and Crohn's disease awaits identification of the genetic factors responsible for the failure to down-regulate the mucosal immune response to a ubiquitous or pathogenic luminal constituent.

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