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Review

Treatment of inflammatory bowel disease (IBD)

Anand B. Pithadia, Sunita Jain

Department of Pharmacology, L.M. College of Pharmacy, Navrangpura, Ahmedabad-3800 09 Gujarat, India

Correspondence: Anand B. Pithadia, e-mail: abpithadia@hotmail.com

Abstract:
Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, which includes Crohn's disease (CD) and ulcerative colitis (UC). These diseases have become important health problems. Medical therapy for IBD has advanced dramatically in the last decade with the introduction of targeted biologic therapies, the optimization of older therapies, including drugs such as immunomodulators and 5-aminosalicylic acid (5-ASA), and a better understanding of the mucosal immune system and the genetics involved in the pathogenesis of IBD. The goal of IBD therapy is to induce and maintain remission. The current treatment paradigm involves a step-up approach, moving to aggressive, powerful therapies only when milder therapies with fewer potential side effects fail or when patients declare themselves to have an aggressive disease. This review focuses on the current treatments for inflammatory bowel disease.

Key words:
inflammatory bowel disease (IBD), 5-aminosalicylates, corticosteroids, infliximab

Abbreviations: 5-ASA – 5-aminosalicylic acid, CD – Crohn's disease, CDAI – Crohn's disease activity index, CRP – C-reactive protein, DHA – docosahexaenoic acid, DNBS – 2,4-dinitrobenzene sulfonic acid, EPA – eicosapentaenoic acid, IBD – inflammatory bowel disease, IgE – immunoglobulin E, IL – interleukin, MMF – mycophenolate mofetil, NF-κB – nuclear factor kappa B, SCG – sodium cromoglycate, TNF – tumor necrosis factor, UC – ulcerative colitis

Introduction

Inflammatory bowel diseases (IBDs), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract and are characterized by chronic recurrent ulceration of the bowels [16]. IBD causes significant gastrointestinal symptoms, including diarrhea, abdominal pain, bleeding, anemia, and weight loss. IBD is associated with a spectrum of extraintestinal manifestations, including arthritis, ankylosing spondylitis, sclerosing cholangitis, uveitis, iritis, pyoderma gangrenosum, and erythema nodosum. The pathogenesis of IBD likely involves genetic, environmental, and immunological factors [9, 16, 36]. Macrophages play a primary role in the formation of noncaseous epithelioid granulomas in the intestinal mucosa. Activated macrophages produce cytokines, such as TNF-α, interleukins (IL-6, IL-8), and others [44]. Current drug treatments aim to induce and maintain the patient in remission and ameliorate the disease's secondary effects, rather than modifying or reversing the underlying pathogenic mechanism [21]. Corticosteroids, aminosalicylates, and immunosuppressive agents, such as azathioprine, are routinely used [24]. Other drugs, such as metronidazole and broad-spectrum antibiotics, are helpful in some cases, while colestyramine, sodium cromoglycate, bismuth and arsenical salts,

methotrexate, and fish oils provide alternative therapies. A new approach for the treatment of IBD using humanized monoclonal antibody preparations has produced encouraging results and may eventually provide a welcome alternative to traditional treatments because these antibody treatments modify the affected biochemical inflammatory pathways. Some specific goals of pharmacotherapy in IBD include controlling acute exacerbation of the disease, maintaining remission, and treating specific complications such as fistulas. Specific drugs may be better suited to one or more of these aims. For example, steroids are the treatment of choice for moderate to severe flare-ups but are inappropriate for long-term use because of their side effects and inability to maintain remission. Other immunosuppressants, such as azathioprine, that require several weeks to achieve their therapeutic effect have a limited role in the acute setting but are preferred for long-term management [45]. A more thorough appreciation of the intricacies of the inflammatory response and improved biotechnology has led to the development of biological agents that can target single steps in the immune cascade. Drug delivery to the appropriate site(s) along the gastrointestinal tract also has been a major challenge, and second-generation agents have been developed with improved drug delivery, increased efficacy, and decreased side effects.

Treatment of IBD

Aminosalicylates

Aminosalicylates can be used in combination with steroids to induce and maintain remission in patients with inflammatory bowel disease. The first-line therapy for mild to moderate UC generally involves mesalamine (5-aminosalicylic acid, or 5-ASA). The archetype for this class of medications is sulfasalazine, which consists of 5-ASA linked to sulfapyridine by an azo bond. Although this drug was originally developed as a treatment for rheumatoid arthritis, clinical trials serendipitously demonstrated a beneficial effect on the gastrointestinal symptoms of subjects with concomitant UC. Sulfasalazine is most effective at maintaining remission in UC. When it reaches the colon, the diazo bond is cleaved by bacterial azoreductase, liberating mesalamine and sulfapyridine. Sulfapyridine is absorbed and metabolized by hepatic acetylation or hydroxylation followed by glucuronidation. Given individually, either 5-ASA or sulfapyridine is absorbed in the upper gastrointestinal tract; the azo linkage in sulfasalazine prevents its absorption in the stomach and small intestine, and the individual components are not liberated for absorption until colonic bacteria cleave the bond. 5-ASA is the active therapeutic moiety; sulfapyridine contributes little to the therapeutic effect. Although mesalamine is a salicylate, its therapeutic effect does not appear to be related to cyclooxygenase inhibition; indeed, traditional nonsteroidal anti-inflammatory drugs may actually exacerbate IBD. Many potential sites of action have been demonstrated *in vitro* for either sulfasalazine or mesalamine, including inhibition of IL-1 and TNF-α production, inhibition of the lipoxygenase pathway, the scavenging of free radicals and oxidants, and inhibition of NF-κB (nuclear factor kappa B), a transcription factor pivotal to the production of inflammatory mediators [3]. Although it is not active therapeutically, sulfapyridine causes many of the same side effects observed in patients taking sulfasalazine. To preserve the therapeutic effect of 5-ASA without the side effects of sulfapyridine, several second-generation 5-ASA compounds have been developed. They are divided into two groups: prodrugs and coated drugs. Prodrugs contain the same azo bond as sulfasalazine but replace the linked sulfapyridine with either another 5-ASA (olsalazine) or an inert compound (balsalazide). These compounds act at similar sites along the gastrointestinal tract as sulfasalazine. The alternative approaches employ either a delayed-release formulation or a pH-sensitive coating. Delayed-release mesalamine is released throughout the small intestine and colon, whereas pH-sensitive mesalamine is released in the terminal ileum and colon. The different distributions of these drugs following delivery have potential therapeutic implications.

Oral sulfasalazine has been shown to be effective in patients with mild or moderately active UC, with response rates between 60 and 80% [46]. The usual dose is 4 g/day, which is divided into four separate doses taken with food; to avoid adverse effects, the dose is increased gradually from an initial dose of 500 mg twice a day. Doses as high as 6 g/day can be used, but these doses cause an increased incidence of side effects. For patients with severe colitis, sulfasalazine is of less certain value even though it is often used as an adjunct therapy to systemic glucocorticoids. Regardless of disease severity, this drug plays a useful

role in preventing relapses once remission has been achieved. In general, newer 5-ASA preparations have similar therapeutic efficacies in UC with fewer side effects. Because they lack the dose-related side effects of sulfapyridine, the newer formulations can be used to provide higher doses of mesalamine, which leads to some improvement in disease control. To treat active diseases, olsalazine is typically administered at a dose of 800 mg three times a day, and balsalazide is generally administered at a 1-g dose given four times a day.

The efficacy of 5-ASA preparations (e.g., sulfasalazine) in CD is less striking, with a modest benefit at best in controlled trials. Sulfasalazine has not been shown to be effective in maintaining remission and has been replaced by newer 5-ASA preparations. Some studies have reported that both olsalazine and balsalazide are more effective than a placebo in inducing remission in patients with CD (particularly colitis), although higher doses than those typically used in UC are required. The role of mesalamine in maintenance therapy for CD is controversial, and there is no clear benefit of continued 5-ASA therapy in patients who achieve medical remission [6]. Because they largely bypass the small intestine, prodrugs such as olsalazine and balsalazide do not have a significant effect in CD of the small intestine.

Topical preparations of mesalamine suspended in a wax matrix suppository or in a suspension enema are effective in active proctitis and distal UC, respectively [64]. They appear to be superior to topical hydrocortisone in this setting, with response rates of 75 to 90%. Mesalamine enemas (4 g/60 ml) should be used at bedtime and retained for at least eight hours; the suppository (500 mg) should be used two to three times a day with the objective of retaining it for at least three hours. Responses to local therapy with mesalamine may occur within three to 21 days; however, the usual course of therapy is from three to six weeks. Once remission has occurred, lower doses are used for maintenance.

Side effects of sulfasalazine occur in 10 to 45% of patients with UC and are primarily related to the sulfa moiety. Some side effects are dose-related, including headache, nausea, and fatigue. These reactions can be minimized by administering the medication with meals or by decreasing the dose. Allergic reactions include rash, fever, Stevens-Johnson syndrome, hepatitis, pneumonitis, hemolytic anemia, and bone marrow suppression. Sulfasalazine reversibly decreases the number and motility of sperm but does not impair female fertility. It also inhibits intestinal folate absorption; therefore, folate usually is given with sulfasalazine. The newer mesalamine formulations are generally well tolerated, and side effects are relatively infrequent and minor. Headache, dyspepsia, and skin rash are the most common side effects. Diarrhea appears to be particularly common with olsalazine (occurring in 10 to 20% of patients); this may be related to its ability to stimulate chloride and fluid secretion in the small intestine. Nephrotoxicity, although rare, is a more serious concern. Mesalamine has been associated with interstitial nephritis; while its pathogenic role is controversial, renal function should be monitored in all patients receiving these drugs. Both sulfasalazine and its metabolites cross the placenta but have not been shown to harm the fetus. Although they have not been studied as thoroughly, the newer formulations also appear to be safe during pregnancy [41].

Corticosteroids

The glucocorticoid properties of hydrocortisone and prednisolone are the mainstay of IBD treatment. The preferred steroid is prednisolone, administered orally, rectally or parenterally in emergency situations. Corticosteroids can be used either alone or in combination with a suitable mesalamine formulation to induce and maintain remission in inflammatory bowel disease. The incidence of adverse effects appears to increase when prednisolone doses are higher than 40 mg/day. An alternate-day regimen is helpful because it reduces adrenal suppression. Azathioprine, with its steroid-sparing property, may be introduced together with a lower dose of steroids [41]. The response to steroids in individual patients with IBD divides them into three general classes: steroid-responsive, steroid-dependent, and steroid-unresponsive. Steroid-responsive patients improve clinically, generally within one to two weeks, and remain in remission as the dose of steroids is tapered and discontinued. Steroid-dependent patients also respond to glucocorticoids but experience a relapse of symptoms as the steroid dose is tapered [1]. Steroid-unresponsive patients do not improve even with prolonged high doses of steroids. Approximately 40% of patients are steroid-responsive, 30 to 40% have only a partial response or become steroid-dependent, and 15 to 20% of patients do not respond to steroid therapy. Steroids are sometimes used for prolonged periods to control symptoms in steroid-dependent patients. However, failure to respond to steroids with prolonged remission (i.e., a disease re-

lapse) should prompt consideration of alternative therapies, including immunosuppressants and infliximab. Steroids are not effective in maintaining remission in either UC or CD [58]; thus, their significant side effects have led to an increased emphasis on limiting the duration and cumulative dose of steroids in IBD.

Initial doses for prednisone is between 40 to 60 mg per day; higher doses are rarely more effective [4]. The glucocorticoid dose is tapered over weeks to months. Even with this slow tapering, efforts should be made to minimize the duration of steroid therapy. In severely ill hospitalized patients, 100 mg of hydrocortisone administered intravenously every eight hours is a reasonable initial therapy. Intravenous therapy generally produces a rapid improvement of symptoms, with maximal benefits occurring when the corticosteroid has been administered for six to eight days. Once the patient's symptoms have improved, prednisone is tapered by 5 to 10 mg per week, until the dosage reaches 15 to 20 mg per day. This dosage is then tapered by 2.5 to 5 mg per week until the drug is discontinued. The goal is to remove patients from corticosteroids within a relatively short period of time while maintaining disease remission. Concomitant use of 5-ASA agents can be helpful. Alternatively, long-term, alternate-day corticosteroid therapy can be used in patients with refractory CD, although it may be necessary to use dosages of 20 to 25 mg every other day [13]. Systemic corticosteroids have an extensive side effect profile. Acute side effects include acne and severe mood changes, which are particularly common in young patients. Adrenal insufficiency can be triggered by an intercurrent infection in patients who are receiving low doses of systemic corticosteroids or in patients who have been recently tapered off of corticosteroids. Visual changes can occur because of steroid-induced hyperglycemia. Early cataract formation is another possible side effect. Aseptic joint necrosis, which is the most dreaded side effect, usually occurs in patients receiving long-term, high-dose corticosteroid therapy. The incidence of this complication is 4.3% [62].

Budesonide is an enteric-release form of a synthetic steroid that is used for ileocecal CD [20]. It is thought to deliver adequate steroid therapy to a specific portion of the inflamed gut while minimizing systemic side effects caused by extensive first-pass hepatic metabolism to inactive derivatives. Topical therapies (e.g., enemas and suppositories) are also effective in treating colitis that is limited to the left side of the colon. While the topical potency of budesonide is 200 times higher than that of hydrocortisone, its oral systemic bioavailability is only 10%. In some studies, budesonide was associated with a lower incidence of systemic side effects than prednisone, although the data also indicate that systemic steroids are more effective in patients with higher CD activity index scores. Budesonide (9 mg/day for 10 to 12 weeks) is effective in the acute management of mild-to-moderate exacerbations of CD, but its role in maintaining remission has not been fully determined [27]. A significant number of patients with IBD fail to respond adequately to glucocorticoids and are either steroid-resistant or steroid-dependent. The reasons for this failure are poorly understood but may involve complications such as fibrosis or strictures in CD, which do not respond to anti-inflammatory measures alone, local complications such as abscesses, in which case the use of steroids may lead to uncontrolled sepsis, and intercurrent infections with organisms such as cytomegalovirus and *Clostridium difficile*. Steroid failures may also be related to specific pharmacogenomic factors, such as up-regulation of the multidrug resistance (*mdr*) gene [12] or altered levels of corticosteroid-binding globulin.

Corticosteroid enemas are beneficial in patients with ulcerative proctosigmoiditis. The foam preparations may facilitate retention and thus may be more effective than the liquid preparations. Both foam and liquid corticosteroid enemas are slightly less effective than 5-ASA enemas and are almost as expensive. Some systemic absorption occurs; adrenal suppression and other corticosteroid side effects rarely occur with long-term use. Glucocorticoid enemas are useful in patients whose disease is limited to the rectum (proctitis) and left colon. Hydrocortisone is available as a retention enema (100 mg/60 ml), and the usual dose is one 60-ml enema per night for two or three weeks. When optimally administered, the drug can reach up to or beyond the descending colon. Patients with a distal disease usually respond within three to seven days.

Hydrocortisone also can be given once or twice daily as a 10% foam suspension that delivers 80 mg hydrocortisone per application; this formulation can be useful in patients with very short areas of distal proctitis and difficulty retaining fluids. Tixocortol pivolate and fluticasone propionate are among the newer corticosteroid analogs currently under investigation. These newer corticosteroids are more rapidly metabolized than traditional corticosteroids, and they offer the promise of efficacy with fewer systemic side effects.

The packaging of these agents in a pH-sensitive coating (similar to that used for 5-ASA preparations) offers the possibility of drug delivery to the small intestine and right colon with few side effects [24].

Immunosuppressants

Several drugs initially developed for cancer chemotherapy or as immunosuppressive agents in organ transplants have been adapted for the treatment of IBD. Immunosuppressant drugs can be an invaluable adjunct therapy for the treatment of patients with intractable inflammatory bowel disease or complex, inoperable perianal disease. Although immunosuppressant agents have significant side effects, they are safer and better tolerated than long-term corticosteroid therapy. However, these agents should not be used in young patients who are candidates for surgery or in patients who are noncompliant and refuse to return for periodic monitoring. Before immunosuppressant therapy is initiated, side effects and other treatment alternatives should be discussed with the patient. At this stage, it is best to set a definable goal, such as closure of a fistula or tapering the patient off of corticosteroids, and a minimum three-month time frame should be set to reach that goal [41].

Since the early 1970s, azathioprine and mercaptopurine have been used to treat IBD. These drugs are superior to the placebo, but their full effects may not become apparent for as long as three months. Azathioprine and mercaptopurine are beneficial in 50 to 70% of patients with intractable perianal CD [1]. Less information is available about their effectiveness in treating UC, although they have been beneficial in patients with this disease. The cytotoxic thiopurine derivatives mercaptopurine (6-MP) and azathioprine are used to treat patients with severe IBD or those who are steroid-resistant or steroid-dependent [45]. These thiopurine antimetabolites impair purine biosynthesis and inhibit cell proliferation. Both are prodrugs; azathioprine is converted to mercaptopurine, which is subsequently metabolized to 6-thioguanine nucleotides, which are the presumed active moiety. These drugs are generally used interchangeably with appropriate dose adjustments; typically, azathioprine is administered at a dose of 2 to 2.5 mg/kg and mercaptopurine is given at a dose of 1.5 mg/kg. Because of concerns of side effects, these drugs were used initially only in CD, which lacks a surgical curative option. They now are considered equally effective in both CD and UC. These drugs effectively maintain remission in both diseases; they may also prevent (or, more typically, delay) recurrence of CD after surgical resection. The decision to initiate immunosuppressive therapy depends on an accurate assessment of the risk to benefit ratio.

For both azathioprine and mercaptopurine, the initial dosage is 50 mg per day. A therapeutic benefit usually occurs at dosages of 50 to 100 mg per day for mercaptopurine and 75 to 150 mg per day for azathioprine. Mild leukopenia suggests that the drug is effective and therefore more likely to benefit the patient. It is prudent to obtain a complete blood count every two weeks during the initial treatment phase in patients with active disease and every three months in patients on maintenance therapy [31]. Drug-induced pancreatitis occurs in 3 to 5% of the patients, invariably during the first six weeks of azathioprine or mercaptopurine therapy [23]. Pancreatitis is a contraindication for continued use of these agents. One large, retrospective review failed to find a significant association between azathioprine and the development of lymphoma or leukemia [8, 17].

For more than 20 years, low-dose methotrexate therapy has been used in patients with intractable psoriasis and rheumatoid arthritis. Methotrexate was engineered to inhibit dihydrofolate reductase, thereby blocking DNA synthesis and causing cell death. First used in cancer treatment, methotrexate was subsequently recognized to have beneficial effects in autoimmune diseases such as rheumatoid arthritis and psoriasis. The anti-inflammatory effects of methotrexate may involve mechanisms in addition to its inhibition of dihydrofolate reductase. One study showed that this treatment was beneficial in 70% of patients with severe IBD [14]. The response to methotrexate appeared to be more rapid than the response to mercaptopurine. Methotrexate is given weekly as an intramuscular injection of 15 to 25 mg. Side effects are rare and include leukopenia and hypersensitive interstitial pneumonitis. Hepatic fibrosis is the most severe potential side effect of long-term therapy. Patients with concomitant alcohol abuse and/or morbid obesity are more likely to develop hepatic fibrosis and therefore should not be treated with methotrexate. It is prudent to obtain a baseline chest radiograph and to monitor the patient's complete blood count, liver function, and renal function every two weeks until the patient is receiving oral therapy and every one to three months thereafter. Before methotrexate therapy is ini-

tiated, the risks of treatment and the possible need for a liver biopsy should be discussed with the patient.

A pretreatment liver biopsy is indicated in patients who have abnormal liver function tests and in those at a potentially increased risk for hepatic toxicity. Follow-up liver function tests are not a good predictor of toxicity. As with azathioprine-mercaptopurine, methotrexate is generally reserved for patients whose IBD is either steroid-resistant or steroid-dependent [30, 45]. In CD, it both induces and maintains remission, generally with a more rapid response than observed with mercaptopurine or azathioprine. Only limited studies have examined the role of methotrexate in UC.

Treatment of IBD with methotrexate differs somewhat from its use in other autoimmune diseases. Most importantly, higher doses (e.g., 15 to 25 mg/week) are given parenterally. The increased efficacy with parenteral administration may reflect the unpredictable intestinal absorption at higher doses of methotrexate. For unknown reasons, the incidence of methotrexate-induced hepatic fibrosis in patients with IBD is lower than that seen in patients with psoriasis [15].

Cyclosporine

The calcineurin inhibitor cyclosporine is a potent immunosuppressant drug used in organ transplantation. Since the mid-1980s, this drug has also been used to treat patients with IBD. At this time, cyclosporine is most useful in severely ill patients with UC who have not responded to corticosteroid therapy. In such patients, intravenously administered cyclosporine is highly effective for rapid disease control, and it may allow patients to avoid surgery. However, after one year, 70 to 80% of these patients may still require surgery. Thus, in many patients, the role of cyclosporine is to change a risky emergency operation into a less urgent procedure [35]. Cyclosporine is effective in specific clinical settings in IBD, but the high frequency of significant adverse effects limits its use as a first-line medication. Cyclosporine is effective in severe UC that has failed to respond adequately to glucocorticoid therapy. Between 50 and 80% of these severely ill patients improve significantly (generally within 7 days) in response to intravenous cyclosporine (2 to 4 mg/kg daily), which sometimes allows them to avoid an emergent colectomy. Careful monitoring of cyclosporine levels is necessary to maintain a therapeutic level in whole blood between 300 and 400 ng/ml.

Oral cyclosporine is less effective as a maintenance therapy in IBD, perhaps because of its limited intestinal absorption. In this setting, long-term therapy with a microemulsion formulation of cyclosporine with increased oral bioavailability may be more effective, but this has not been fully studied. Cyclosporine can be used to treat fistulous complications of CD. A significant, rapid response to intravenous cyclosporine has been observed; however, frequent relapses accompany oral cyclosporine therapy, and other medical strategies are required to maintain fistula closure. Thus, it is generally used to treat specific problems over a short term while providing a bridge to long-term therapy [52]. Cyclosporine is lipid-bound and thus is associated with an increased risk of seizures when it is administered to acutely ill, severely malnourished patients who have low serum cholesterol/lipid levels. Oral maintenance with cyclosporine has, at best, limited benefit, and the relapse rate is high. The drug has a significant side effect profile that includes renal insufficiency and hypertension.

Other immunomodulators that are also being evaluated in IBD include tacrolimus and MMF. Tacrolimus is similar to cyclosporine, but its oral form is better absorbed than oral cyclosporine. It is showing promise in small studies of severe CD. Less than half of patients, however, achieve long-term remission. MMF is being studied as an alternative for Crohn's patients with fistulas who cannot tolerate azathioprine or mercaptopurine. It appears to be roughly equivalent in effectiveness and safety to other agents, although not as effective in maintaining remission. Very small studies have shown a 75% fistula closure rate with an average of eight months of treatment with MMF [24].

Monoclonal antibodies (biologicals)

Biological response modifiers are drugs that interfere with the inflammatory response. Of special interest for the treatment of Crohn's disease and other diseases are drugs that target the inflammatory immune factor known as TNF-α. The administration of humanized monoclonal antibodies is an entirely new and potentially highly successful concept for treating IBD. The first such product, infliximab, is available for treating refractory CD. It acts by inhibiting the functional activity of TNF-α. Following treatment, histological evaluation of colonic biopsies revealed a substantial reduction in detectable TNF-α. Treatment was also associated with a reduction of the commonly ele-

vated serum inflammatory maker CRP. Infliximab is a chimeric immunoglobulin (25% mouse, 75% human) that binds to and neutralizes TNF-α, and it represents a new class of therapeutic agents for treating IBD [60]. Although many pro- and anti-inflammatory cytokines are generated in the inflamed gut in IBD, there is some rationale for targeting TNF-α because it is one of the principal cytokines mediating the T_H1 immune response characteristic of CD. Infliximab (5 mg/kg infused intravenously at intervals of several weeks to months) decreases the frequency of acute flare-ups in approximately two-thirds of patients with moderate to severe CD and facilitates the closing of enterocutaneous fistulas associated with CD [47]. Its long-term role in CD is evolving, but emerging evidence supports its efficacy in maintaining remission [48] and in preventing recurrence of fistulas [54]. Although infliximab was specifically designed to target TNF-α, it also may have more complex actions. Infliximab binds membrane-bound TNF-α and may cause lysis of these cells by antibody-dependent or cell-mediated cytotoxicity. Thus, infliximab may deplete specific populations of subepithelial inflammatory cells. These effects, together with its mean terminal plasma half-life of eight to 10 days, may explain the prolonged clinical effects of infliximab.

The use of inflixamab as a biological response modifier raises several important considerations. Both acute (fever, chills, urticaria, or even anaphylaxis) and subacute (serum sickness-like) reactions may develop after infliximab infusion. Anti-double-stranded DNA antibodies develop in 9% of patients, but a frank lupus-like syndrome occurs only rarely. Antibodies to infliximab can decrease its clinical efficacy; strategies to minimize the production of these antibodies (e.g., treatment with glucocorticoids or other immunosuppressives) may be critical to preserving infliximab efficacy for either recurrent or chronic therapy [11]. Other proposed strategies to overcome the problem of antibody resistance include increasing the dose of infliximab or decreasing the interval between infusions. Infliximab therapy is associated with the increased incidence of respiratory infections; of particular concern in infliximab treatment is the potential reactivation of tuberculosis or other granulomatous infections with subsequent dissemination. It is recommended that candidates for infliximab therapy be tested for latent tuberculosis with purified protein derivatives, and patients who test positive should be treated prophylactically with isoniazid. However, anergy with a false-negative skin test has been noted in some patients with CD, and some experts routinely perform chest radiographs to look for active or latent pulmonary disease. Infliximab is also contraindicated in patients with severe congestive heart failure (New York Heart Association classes III and IV) and should be used cautiously in class I or II patients. As with the immunosuppressant drugs, there are concerns about the possible increased incidence of non-Hodgkin's lymphoma, but a causal role has not been established. Finally, the significant cost of infliximab is an important consideration for some patients [24, 41].

Adalimumab is an anti-TNF agent similar to infliximab and decreases inflammation by blocking TNF-α. In contrast to infliximab, adalimumab is a fully humanized anti-TNF antibody (no mouse protein). Adalimumab is administered subcutaneously instead of intravenously, as in the case of infliximab. Adalimumab is comparable to infliximab in effectiveness and safety for inducing and maintaining remission in patients suffering from Crohn's disease (CD). Adalimumab is also effective in healing anal fistulas in patients with CD. Adalimumab is well tolerated and has been shown to be effective for patients who cannot tolerate infliximab. The most common side effect is skin reactions at the site of injection, such as swelling, itching, or redness. Other common side effects include upper respiratory infections, sinusitis, and nausea. Rare cases of lymphoma and nervous system inflammation have been reported with the use of adalimumab. Symptoms of nervous system inflammation may include numbness and tingling, vision disturbances, and weakness in the legs. Some patients receiving adalimumab may rarely develop symptoms that mimic systemic lupus; these symptoms include skin rash, arthritis, chest pain, or shortness of breath. These lupus-like symptoms resolve after cessation of drug treatment. In a randomized, double-blind, placebo-controlled trial, adalimumab was more effective than the placebo in maintaining clinical remission for patients with moderate-to-severe CD through 56 weeks. In this study, adalimumab demonstrated sustained maintenance of clinical remission, improvements in quality of life, and reductions in hospitalization during long-term treatment for CD, with no new safety concerns identified [43].

Certolizumab pegol is a monoclonal antibody directed against TNF-α. More precisely, it is a PE (polyethylene) gylated Fab' fragment of a humanized TNF-inhibiting monoclonal antibody; this PE gylation increases the

half-life of the drug by up to 14 days. In well-designed Phase III clinical trials, certolizumab pegol was associated with significantly greater response rates compared to the placebo at weeks six and 26 of induction treatment. In patients who responded to the six-week induction, certolizumab pegol, administered as a monthly subcutaneous injection, was effective in maintaining CD treatment response and remission. Findings from studies of certolizumab pegol in refractory CD are currently underway [53].

Agents to reduce symptoms

Antibiotics

There are experimental and clinical data demonstrating that colonic bacteria may either initiate or perpetuate the inflammation of IBD [55, 56]. Metronidazole has been used with some success in CD patients at a dose of 10–20 mg/kg/day. Patients with severe perianal inflammation have responded to metronidazole treatment, experiencing less pain and tenderness, eventually decreased erythema and swelling, and wound healing. Certain bacterial strains may be pro- (e.g., *Bacteroides*) or anti-inflammatory (e.g., *Lactobacillus*), prompting attempts to manipulate the colonic flora in patients with IBD [26]. Traditionally, antibiotics have been used to this end, especially in CD. More recently, probiotics have been used to treat specific clinical situations in IBD. Antibiotics can be used as (1) an adjunctive treatment along with other medications for treatment of active IBD, (2) a treatment for a specific complication of CD, or (3) prophylaxis for disease recurrence in postoperative CD. Metronidazole, ciprofloxacin, and clarithromycin are the antibiotics used most frequently [2, 59]. They are more beneficial in CD of the colon than in disease restricted to the ileum. Specific CD-related complications that may benefit from antibiotic therapy include intra-abdominal abscesses and inflammatory masses, perianal diseases (including fistulas and perirectal abscesses), bacterial overgrowth in the small bowel secondary to partial small bowel obstruction, secondary infections with organisms such as *Clostridium difficile,* and postoperative complications. Metronidazole may be particularly effective for the treatment of perianal disease. Postoperatively, metronidazole and related compounds have been shown to delay the recurrence of CD. In one study, a three-month course of metronidazole (20 mg/kg per day) prolonged the time to both endoscopic and clinical recurrence [49]. The significant side effects of prolonged systemic antibiotic use must be balanced against their potential benefits, and definitive data to support their routine use are lacking. Antibiotics are often used to induce remission in mild to moderate CD. They are also important for treating fistulas, bacterial overgrowth, abdominal abscesses, and infections around the anus and genital areas. Stopping antibiotics induces relapse; as a result, long-term therapy is required, which carries a risk for side effects.

The standard antibiotics used for inducing remission in CD are ciprofloxacin and metronidazole. Ciprofloxacin is the antibiotic of choice. Other antibiotics used for CD include trimethoprim/sulfamethoxazole and tetracycline. Small studies have reported that either ciprofloxacin or metronidazole has produced yearlong remission rates of approximately 70%. Comparison studies with corticosteroids, however, have not clearly identified any additional benefits from antibiotics for mild to moderate CD. Additional research is needed to clarify this issue.

Supportive treatment

Analgesic, anticholinergic, and antidiarrheal agents play supportive roles in reducing symptoms and improving quality of life. These drugs should be individualized based on a patient's symptoms and given in addition to anti-inflammatory medications [57]. Diarrhea continues to be a prevalent symptom in patients with IBD, requiring a wide differential diagnosis to define the pathophysiological mechanisms in individual patients. It is essential that physicians properly evaluate complaints of diarrhea by assessing both the patient's symptoms and the potential physiological impacts on fluid and electrolyte status. Underlying mechanisms of diarrhea with IBD depend on the location, extent, and severity of the inflammation, malabsorption, altered motility, and iatrogenic causes, such as medications, diet, and antibiotic-associated colitis (e.g., *Clostridium difficile*) [28]. Medications, including loperamide, diphenoxylate, codeine sulfate, and tinctures of opium, slow motility and increase the absorption of fluids and nutrients. For iatrogenic issues, medications that cause diarrhea should be withdrawn

and individual diets modified. Not all types of diarrhea in the IBD patient are the same; therefore, it is essential to tailor therapies according to the presumed etiologies. Antidiarrheal agents are not recommended in extremely ill patients and those with known hypersensitivities or evidence of colonic obstruction or dilation, fever, or abdominal tenderness. Concomitant use of loperamide with diphenoxylate and atropine should be avoided in early pregnancy. Loperamide or diphenoxylate can be used to reduce the frequency of bowel movements and relieve rectal urgency in patients with mild disease; these agents are contraindicated in patients with severe disease because they may cause patients to develop toxicity to megacolon anticholinergic agents (e.g., dicyclomine hydrochloride), which are used to reduce abdominal cramps, pain, and rectal urgency. As with the antidiarrheal agents, they are contraindicated in severe disease or when obstruction is suspected. Codeine, diphenoxylate, and loperamide should be used cautiously to treat diarrhea and abdominal cramping in inflammatory bowel disease because their use may mask inflammation, infection, obstruction, or colonic dilatation, thereby delaying an accurate diagnosis.

Cholestyramine can be used to prevent bile salt-induced colonic secretions in patients who have undergone limited ileocolic resections. Following ileal resection, colestyramine has been used in CD to decrease diarrhea associated with bile-acid malabsorption caused by the decrease in the small bowel absorptive surface area and the cathartic effect of bile salts on the colon. At doses of up to 4 g three times a day, it inhibits bile-acid stimulated secretion of water and electrolytes.

Sodium cromoglycate

Sodium cromoglycate (SCG) reduces degranulation of mast cells by inhibiting the passage of calcium ions across cell membranes, a process essential for the release of inflammatory mediators from mast cells. Intestinal lesions contain mast cells, macrophages, and eosinophils, and rectal biopsies show large numbers of IgE plasma cells in the lamina propria. SCG was applied intrarectally for the treatment of UC in 39 patients with an active pathological process. The drug was insufflated by means of a rectoscopic tube at a dosage of 200 mg daily for 15 days. Complete remission of the disease was achieved in 97% of patients within two weeks of the administration of the drug. As a maintenance treatment, the patients were given SCG orally (240 mg daily) for a period of two to three years. During the course of two to three years of observation, 93% of the patients showed remission maintenance due to oral SCG therapy [38].

Bismuth salts

Bismuth subsalicylate citrate and bismuth chelate, administered as enemas, are effective treatments for UC. Bismuth salts inhibit sulfatase and sialidase enzymes, which are secreted by colonic bacteria, and contribute to the process of mucus degradation. Bismuth also demonstrates cytoprotective properties through a mechanism that increases tissue prostaglandin levels. In a prospective open study, 15 patients with UC who were unresponsive to conventional therapy were treated with enemas containing bismuth subsalicylate (700 or 800 mg daily). Nine out of the 15 patients showed a significant clinical response, and six went into complete clinical remission after eight weeks of treatment. Sigmoidoscopic appearances of the rectal mucosa showed improvement in nine out of 15 patients at two weeks, and 11 out of 15 patients at eight weeks. The mucosa appeared normal in six out of 15 patients at eight weeks. A reduction in the oral prednisolone dosage from a median of 15 mg daily (range 10 to 35 mg daily) to 6 mg daily (range 0 to 18 mg daily) was also shown to be effective after eight weeks of treatment; five patients were no longer taking oral steroids at this time. Rectal bismuth subsalicylate appears to be an effective therapy in UC and controlled trials are now required. Similarly, arsenic salts, particularly acetarsol in the form of 250 mg suppositories, have been used successfully to treat 172 patients with ulcerative proctitis, but their toxicity limits their use. Acetarsol is bactericidal and chemically similar to bismuth, which may account for its method of action [50].

Thalidomide

The use of thalidomide has been restricted to monitored refractory cases of CD [38]. It acts as a TNF-α inhibitor and probably stabilizes lysosomal membranes. Additionally, at therapeutic doses, thalidomide inhibits the formation of superoxide and hydroxyl radicals, which are potent oxidants capable of causing tissue damage. Thalidomide treatment (200 mg/kg per oral) reverses the development of experimental colitis induced by DNBS in mice [39]. This evidence may

help to clarify the therapeutic actions of thalidomide in patients with CD. The safety, tolerance, and efficacy of low dosages of thalidomide were evaluated for the treatment of moderate-to-severe, steroid-dependent CD. For this study, 12 adult male patients with CD activity index (CDAI) scores of greater than or equal to 250 or less than or equal 500 despite administration of greater than or equal to 20 mg prednisone/day were enrolled. Six patients received 50 mg thalidomide every night, and six patients received 100 mg every night. Steroid doses were stable during the first four weeks of treatment and were then tapered during weeks 5–12. The CDAI scores were used to assess their responses to the drugs. Disease activity improved consistently in all patients during weeks 1–4 with 58% patients showing a response and 17% patients showing remission. Clinical improvement was generally maintained despite steroid reduction during weeks 5–12. All patients were able to reduce their steroid treatments by greater than or equal to 50%. Forty-four percent discontinued steroids entirely. During weeks 5–12, 70% of patients responded and 20% achieved remission. Side effects were mild and mostly transient; the most common side effects were drowsiness, peripheral neuropathy, edema, and dermatitis. Thus, low doses of thalidomide appear to be well tolerated and effective over a 12-week period. Results of this pilot study support the need for controlled multicenter trials of thalidomide for the treatment of CD [63].

Fish oils

Fish liver oils, which contain EPA and DHA, have been used with some success in the treatment of both UC and CD. UC is accompanied by an increased level of leukotriene B4 in the lining of the colon. Fish oils are known to inhibit the synthesis of leukotrienes. It has therefore been postulated that fish oils might be beneficial in the treatment of UC. One study evaluated the responses of 11 male patients aged 31 to 74 years who had been diagnosed with UC [37]. The patients were randomized into two groups with one group receiving 15 fish oil capsules (providing 2.7 g of EPA and 1.8 g of DHA daily); the other group received placebo capsules (olive oil). After three months on the supplements, all participants underwent a two-month wash-out period and were then assigned to the opposite treatment from what they had received during the first stage for another three months [40]. Clinical evaluations of all of the patients were performed at the start of the study and every month thereafter. Evaluation of the patients' clinical data at the end of the treatment periods showed a significant beneficial effect of fish oil supplementation. The mean disease severities score for the patients on fish oil declined by 56% as compared to 4% for the placebo group. Eight of the 11 patients (72%) were able to markedly reduce or totally eliminate their use of anti-inflammatory medications and steroids while taking the fish oils. It was concluded that fish oil supplementation results in a marked clinical improvement of active mild to moderate UC [25].

Natural remedies for UC

IBD reduces the quality of life, and conventional therapies are not totally successful in preventing relapse or achieving remission. Many herbal remedies have been suggested to be effective in chronic inflammatory conditions; however, there is little clinical or pharmacological data to support these claims. Reactive oxygen metabolites are present in excess in the inflamed colonic mucosa (lining of the colon) and are likely to play a role in inflammation. Therapies that have antioxidant activity may be clinically useful [42, 61]. Herbal therapies are popular among patients with UC; however, they should complement, not replace, conventional care. We discuss some natural remedies used for UC below.

Probiotics

Probiotics are a mixture of putatively beneficial lyophilized bacteria that are given orally. Although probiotics are a promising alternative to more conventional therapies for inflammatory bowel disease, their role in treating IBD requires further evaluation. In one study, they diminished the occurrence of pouchitis, a common inflammatory condition that occurs in surgically created ileal reservoirs after total proctocolectomy for the treatment of UC [19]. Probiotics reside in the gut and have been found to be effective in managing UC. Additionally, they help to control the number of potentially harmful bacteria, reduce inflammation, and improve the protective mucus lining of the gut [10]. Probiotics are among the more popular remedies because they are without significant side effects and appear to be safe [26]. In one study, 34 people with mild-to-moderate active UC who were

unresponsive to conventional treatment were examined. They were treated with probiotic supplements, which provided a total of 3,600 billion bacteria a day, for six weeks [5, 29]. At the end of the study, 18 people (53%) demonstrated remission on sigmoidoscopy, and eight people (24%) had a favorable response. Another study analyzed bacteria from the rectal biopsies of patients with active UC and healthy control subjects. There were significantly less bifidobacterium numbers in the UC biopsies, which suggested that these probiotic bacteria might have a protective role in UC. In a further study, 18 people with active UC were given a bifidobacterium supplement or a placebo for one month. Sigmoidoscopy, biopsy, and blood tests showed significant improvement in the probiotic group compared to the placebo group [18]. The probiotic yeast *Saccharomyces boulardii* was found to be beneficial in the maintenance of CD [22].

Oral *Aloe vera* gel

Aloe vera gel has been demonstrated to have an anti-inflammatory effect. A double-blind, randomized trial examined the effectiveness and safety of *Aloe vera* gel for the treatment of mild-to-moderate active UC. Thirty patients were treated with 100 ml of oral *Aloe vera* gel, and 14 patients were treated with 100 ml of a placebo twice daily for four weeks. Clinical remission, improvement, and responses occurred in nine (30%), 11 (37%), and 14 (47%) patients treated with aloe vera, respectively, compared to one (7%), one (7%), and two (14%) patients, respectively, who received the placebo [33, 34].

Boswellia

Boswellia is an herb that comes from a tree native to India. The active ingredient is the resin from the tree bark, which has been found to block chemical reactions involved in inflammation. It is used by people with UC, rheumatoid arthritis, and other inflammatory conditions. Unlike anti-inflammatory medications, boswellia does not appear to cause the gut irritation that occurs with many conventional pain relievers. A study of people with UC found that 82% of those who took 350 mg of boswellia extract three times daily experienced remission. Rare side effects of boswellia include diarrhea, nausea, and skin rash [32].

Diet

A Japanese study evaluated the role of dietary factors on IBD. Included in the study were 111 people with UC who were given food questionnaires. The survey found that a higher consumption of sweets was positively associated with UC risk. Vitamin C was found to have a protective effect. A higher intake of vitamin C was associated with a lower risk of developing UC. Another study monitored UC patients in remission for one year using food questionnaires. Consumption of meat, particularly red and processed meat, protein, and alcohol increased the likelihood of relapse. It was speculated that the high sulfur or sulfate compounds in many of these foods was the culprit because high sulfur or sulfate intakes were also associated with relapse. Carbohydrates may promote UC in some people. Carbohydrates, which are forms of sugar, may promote and fuel the growth of bacteria and yeast in the intestines, causing an imbalance of microorganisms in the intestines and eventual overgrowth of bacteria and yeast. Bacteria and yeast produce toxins and acids that injure the intestinal lining and impair the function of digestive enzymes, which inhibits the digestion and absorption of carbohydrates and may result into colon inflammation [51].

Folic acid

Patients with chronic UC are at greater risk of colon cancer. It was demonstrated that dietary folate supplementation at four times the basic dietary requirement significantly suppressed UC-associated colon cancer. The incidence of high-grade lesions in the folate-supplemented group was 46% lower than in the control group [7].

Treatment of IBD during pregnancy

Pregnancy is usually uneventful in patients with quiescent IBD. Patients with an active disease are more likely to have a miscarriage, to deliver prematurely, or to have an infant with a below-normal birth weight. However, medical management results in a satisfactory outcome in most of these pregnancies [41]. Radiological studies should be avoided in pregnant women. If possible, flexible sigmoidoscopy should also be avoided because it may stimulate premature labor. In most patients, the risks to the newborn from untreated disease are much greater than the risks associated with medical therapy. For many years, corticos-

teroids and sulfasalazine have been used safely in pregnant women with an active disease. The sulfapyridine moiety of sulfasalazine is tightly bound to serum proteins and therefore does not appear to increase the risk of kernicterus. A review of 5-ASA compounds in pregnancy suggests that they are also safe. Metronidazole has been shown to be potentially teratogenic in animal studies. However, a recent meta-analysis of short-term metronidazole therapy (seven to 10 days) in pregnant women with trichomonas infection suggested that the drug can be used in the first trimester without an increased risk of teratogenicity [24].

If possible, immunosuppressant drugs should not be given to pregnant women. However, azathioprine and mercaptopurine do not appear to increase the risk of congenital malformations in pregnant patients with severe inflammatory bowel disease. Methotrexate probably should not be used in pregnant women with inflammatory bowel disease because little is known about the effects of the drug in pregnancy. IBD is a chronic disease that affects women in their reproductive years; thus, the issue of pregnancy often has a significant impact on medical management. In general, decreased disease activity increases fertility and improves pregnancy outcomes. At the same time, limiting medication during pregnancy is always desired but sometimes conflicts with the goal of controlling the disease.

Mesalamine and glucocorticoids are used frequently during pregnancy and generally are considered safe, whereas methotrexate is clearly contraindicated in pregnant patients. The use of thiopurine immunosuppressants is more controversial. Because these medications are given long term, both their initiation and discontinuation are major management decisions. Although there are no controlled trials of these medications in pregnancy, considerable data have emerged over the last several years. There does not appear to be an increase in adverse outcomes in pregnant patients maintained on thiopurine-based immunosuppressants [17]. Nonetheless, decisions regarding the use of these medications in patients contemplating pregnancy are complex and must involve consideration of the risks and benefits involved.

Summary

IBD is a multifactorial disorder of unknown etiology. The treatment of IBD in any given patient may have several different goals, such as relief of symptoms, induction of remission in patients with active disease, prevention of relapse, healing of fistulas, and avoidance of emergency surgery. The current drug treatments include the use of anti-inflammatory agents and agents that reduce the symptoms associated with IBD. Therapy may be modified to some extent based on the severity and location of the disease. Acute exacerbations of UC are treated with colonic-release preparations of 5-ASA and, in most patients with significant inflammation, with glucocorticoids. For milder cases involving only the rectum, these drugs may be given topically (by enema). In patients who relapse on these preparations, purine metabolites (e.g., azathioprine-mercaptopurine) may be used. The role of 5-ASA preparations in maintenance therapy of CD is limited. Patients who relapse frequently may be treated with immunosuppressant agents (azathioprine-mercaptopurine or methotrexate). Steroid-dependent patients may be treated with long-term budesonide. Infliximab is particularly useful in closing fistulas associated with CD. Its role in maintaining patients in remission is currently being evaluated but must be balanced against the risk of side effects. Antibiotics, particularly metronidazole, may be useful adjuncts for the acute treatment of complications associated with CD (including perianal disease), but these drugs have not been established as a routine therapy for treating this disorder. Other approaches currently being tested in this setting include the use of probiotic bacteria, thalidomide, and drugs from plant sources.

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