Medical Treatment of Ulcerative Colitis

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ABSTRACT

Ulcerative colitis is a chronic inflammatory disease of the colon with an increasing incidence worldwide. The medical management of this disease continues to expand as drugs to induce and maintain remission are sought to avoid the need for colectomy. This article will review the standard of care for the treatment of mild, moderate, and severe ulcerative colitis. The efficacy, optimal usage, and adverse events profile of agents such as 5-aminosalicylates, corticosteroids, azathioprine, and cyclosporine will be discussed and an algorithm for their use will be developed. Alternative and experimental therapies such as monoclonal antibodies, probiotics, and heparin will also be addressed.

KEYWORDS: Ulcerative colitis, medical therapy, cyclosporine

Objectives: Upon completion of this article, the reader should be able to: (1) summarize the standard therapies for mild, moderate, and severe ulcerative colitis; (2) develop an algorithm for the use of medications for the treatment of mild, moderate, and severe ulcerative colitis; and (3) list alternative therapies for ulcerative colitis that have anecdotal evidence of efficacy.

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon that affects up to 12 per 100,000 people in Western countries.[1] The incidence may be increasing in developing nations but is more frequent in Caucasians and people of Jewish descent. Although there is an increase in families, the genetic trend is not as strong as in Crohn's disease.[2] The peak age of incidence is in persons between 15 and 30 years old.[1] Protective factors against the development of UC include cigarette smoking[3] and appendectomy.[4]

The distribution of disease at diagnosis varies widely. Estimates from a Norwegian study report proctitis in 32% of patients, left-sided colitis in 33%, and more extensive colitis in 35%.[5] Thirty-nine percent of patients with proctosigmoiditis can expect extension of their disease[6] and 90% of all UC cases can expect a relapsing course.[7] Approximately 4 to 9% will require colectomy in the year of diagnosis,[5,6] with a subsequent risk of colectomy at 1% per year.[7] The majority of UC patients will require medical therapy chronically throughout their lifetime; therefore, an understanding of the appropriate use of these agents is important for the physician caring for these patients.

Prior to initiating therapy, a patient must be evaluated for extent and severity of disease. Extent of disease is best assessed by colonoscopy with biopsy of grossly affected as well as unaffected areas. If disease is distal to the splenic flexure, topical therapy such as suppositories and enemas may be the first choice. For more extensive disease, oral agents or a combination of oral and topical agents are indicated. The severity of disease can be assessed by the Truelove and Witts score[8] (Table 1). This article will focus on medications for induction and maintenance of remission in mild to moderate UC as well as colectomy-sparing therapy for severe colitis.

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Table 1 Truelove and Witts' Criteria for Evaluating the Severity of Ulcerative Colitis[8]

Variable	Mild Disease	Severe Disease	Fulminant Disease
Stools (number/day)	<4	>6	>10
Blood in stool	Intermittent	Frequent	Continuous
Temperature (°C)	Normal	$>37.5°$	$>37.5°$
Pulse (beats/minute)	Normal	>90	>90
Hemoglobin	Normal	$<75\%$ of normal value	Transfusion required
Erythrocyte sedimentation rate (mm/hr)	$\leqslant 30$	>30	>30
Colonic Features on x-ray		Air, edematous wall, thumbprinting	Dilatation
Clinical signs		Abdominal tenderness	Abdominal distention and tenderness

Moderate disease includes features of both mild and severe disease.

AMINOSALICYLATES

Sulfasalazine and 5-aminosalicylate (5-ASA) drugs are the first line in drug therapy for the treatment of mild to moderate UC. Table 2 summarizes the available agents. Type and dose of therapy are determined by location and severity of disease. For distal disease, topical therapy is the most effective method of delivery. By metanalysis, rectally administered 5-ASA is superior to placebo and rectal corticosteroids for induction and maintenance of remission in distal UC.[9] If the patient has proctitis, 5-ASA suppositories at a dose of 500 mg twice daily will induce and maintain remission.[10,11] For disease up to the splenic flexure, 5-ASA enemas are effective for induction and maintenance of remission in doses of 2 to 4 g per enema.[12,13]

For more extensive disease, multiple oral 5-ASA preparations are available. Sulfasalazine was the first 5-ASA agent found to be effective in UC.[14] Placebo-controlled trials have shown that sulfasalazine is effective in inducing[15,16] and maintaining[17,18] remission in mild to moderate UC. However, its use is limited by high rates of intolerance among patients. Side effects can include headache, abdominal pain, nausea, vomiting, skin rash, fever, hepatitis, hematologic abnormalities, folate deficiency, pancreatitis, systemic lupus erythematosus, and male infertility.[19] Sulfasalazine should always be given with folate 1 mg daily and is contraindicated in men attempting conception.[20]

Sulfasalazine is a combination of 5-ASA azo-bound to the antibiotic sulfapyridine. It is the 5-ASA component that is the therapeutically active compound and the sulfapyridine moiety that is the cause of many of the side effects.[21–23] This finding led to the development of alternative 5-ASA delivery systems for the treatment of UC and the discovery that it is the overall dose of mesalamine given, rather than the delivery system, that determines efficacy. Oral mesalamine agents with delayed- (Asacol) or timed-release (Pentasa) formulations at doses of 1.6 to 4.8 g/day are effective in inducing remission in mildly to moderately active UC.[24–26] Doses of 0.8 to 4.8 g/day are effective in maintaining remission. Combination therapy, with oral mesalamine 2.4 g/day and rectal mesalamine 4 g/day, is more effective than either therapy alone.[27] However, this may simply be a reflection of the overall dose of mesalamine received by the patient.

Olsalazine and balsalazide are 5-ASA agents that have diazo bonds, which are released by colonic bacteria. Olsalazine is effective for induction[28,29] and maintenance[30,31] of remission in UC, but its use is limited

Table 2 5-ASA Preparations

Generic Name	Proprietary Names	5-ASA Delivery Mechanism	Sites of Delivery	Daily Dose, Range
Mesalamine	Rowasa, Salofalk	Enema suspension	Left colon and rectum	1–4 g
Mesalamine	Canasa	Suppository	Rectum	0.5–1.5 g
Mesalamine	Asacol	Eudragit-S coated tablets (release at $pH>7$	Terminal ileum, colon	1.6–4.8 g
Mesalamine	Salofalk, Mesasal, Claversal	Mesalamine in sodium/glycerine buffer coated with Eudragit-L (release at $pH>6$)	Distal jejunum, proximal ileum	1.5–4 g
Mesalamine	Pentasa	Ethylcellulose coated microgranules (time and pH dependant release)	Entire small bowel, colon	2–4 g
Sulfasalazine	Azulfidine	5-ASA azo-bound to sulfapyridine	Colon	1–4 g
Olsalazine	Dipentum	5-ASA dimer linked by azo-bond	Colon	1–3 g
Balsalazide	Colazaal	5-ASA azo-bound to inert carrier	Colon	2–6.75 g

by worsened diarrhea.[32] Balsalazide is composed of a 5-ASA linked to an inert carrier molecule. Although one study did show significant efficacy of balsalazide over an equivalent dose of mesalamine,[33] other studies have shown an efficacy equal to sulfasalazine[34] and mesalamine[35,36] for induction of remission in mild to moderate UC.

Though 5-ASA agents are considered safe, some toxicity can be seen. Aside from the complications attributed to sulfasalazine above, the most frequently reported side effects of 5-ASA agents include dizziness, fever, headache, abdominal pain, nausea, and rash.[25,26] Rare but serious adverse events include pulmonary toxicity, pericarditis, hepatitis, pancreatitis, aplastic anemia, leukopenia, and thrombocytopenia.[37–40] Though interstitial nephritis has been reported,[41] the frequency of renal insufficiency was low in large safety and pharmacovigilance databases for Asacol and Pentasa.[42,43] Finally, a minority of patients will experience worsening diarrhea and abdominal pain due to a hypersensitivity reaction to 5-aminosalicylate.[43a]

In summary, 5-ASA agents are safe and effective for the induction and maintenance of remission in mild to moderate UC. Its use in severe colitis is not well studied. Data support the concept that the optimum use of aminosalicylates in active UC demands the highest tolerated dose, whether administered orally, rectally, or in combination. In quiescent disease, lower doses may be more tolerable to the patient and are less costly, although again, there is the general theme of dose response.

CORTICOSTEROIDS

The discovery that corticosteroids were effective in UC had a significant positive impact on a disease with a previous high mortality. Mortality rates dropped from a high of 61%[44] to 4 to 7%.[45] However, today the side effects of corticosteroids make it a less desirable though sometimes unavoidable agent in the therapy of UC.

In a population-based study in Olmstead County, Minnesota, 34% of UC patients required corticosteroids at some point in their disease course.[46] Therapy with corticosteroids resulted in complete remission in 54%, partial remission in 30%, and no response in 16%. At 1 year from initiation of corticosteroid therapy, prolonged response without steroids or surgery was seen in 49%, corticosteroid dependence in 22%, and surgery in 29%.

Resistance to corticosteroids is seen in 16 to 20% of patients.[46,47] Several potential mechanisms for resistance to corticosteroid therapy in patients with inflammatory bowel disease (IBD) have been described, including an increase in the expression of glucocorticoid receptor β[48] and increased expression of the multidrug resistance-1 gene (MDR-1). The latter results in an increased expression of the membrane-based drug efflux pump P-glycoprotein 170 that pumps corticosteroids out of cells, thus lowering the intracellular concentration.[49]

Corticosteroids can be administered as oral (cortisone, prednisone, prednisolone, budesonide), intravenous (prednisolone, methylprednisolone, corticotropin), or rectal (beclomethasone, tixicortol, budesonide, prednisolone metasulfobenzoate) formulations. Truelove and Witts reported the efficacy of cortisone 100 mg per day in UC in 1955.[8] Baron and colleagues then reported that 40 mg of prednisone was more effective than 20 mg and equally effective as 60 mg, but with fewer side effects.[50] Finally, single daily dosing of prednisone 40 mg daily was equally effective as 10 mg four times a day.[51] It is from these early studies that the current maxim of prednisone 40 mg per day for moderate to severe UC originated. No maintenance benefit of corticosteroids in UC has been found.[52]

Rectal corticosteroids are effective in left-sided UC. They provide quick relief for patients with tenesmus and bleeding. Rectal hydrocortisone 100 mg[53] and prednisolone 10 mg[54] have been proven effective by controlled trials for induction of remission, but not for maintenance.[55] Budesonide enemas, which have minimal systemic absorption, are also effective for induction but not for maintenance of remission in left-sided UC.[56] However, by metanalysis, topical corticosteroids were not as effective as topical mesalamine therapies for ulcerative proctitis and left-sided UC.[57] Also, rectal corticosteroids are well absorbed and can result in suppression of the adrenal axis.[58]

Prednisone and prednisolone are well absorbed after oral administration and bioavailability is high, averaging over 70%. However, the absorption may be decreased in patients with severe UC in whom oral administration of prednisolone resulted in a lower peak plasma concentration and a slower rate of decrease in the plasma concentration compared with healthy volunteers.[59] Patients with severe UC who receive 60 mg/day of intravenous prednisolone have a 73% response rate in 5 days.[60] Some patients are slower responders and will require 7 to 10 days to respond. No controlled trials have addressed the effectiveness of single, multiple, or continuous infusion of corticosteroids in severe UC.[61] Intramuscular corticotropin (adrenal corticotropin hormone, ACTH) at 80 U/day showed a similar benefit to cortisone 200 mg/day in patients with active UC.[55] In severe UC, corticotropin 80 to 120 U/day was similar to hydrocortisone 300 to 400 mg/day.[62–64] However, some deaths were reported in IV ACTH due to adrenocortical necrosis.[64]

Corticosteroid toxicity is frequent and often results in resistance on the part of patients to reinitiate therapy if they have used it before. Short-term toxicities observed include moon face (47%), acne (30%), infection (27%), ecchymoses (17%), hypertension (15%),

Table 3 Adverse Effects Associated with Systemic Corticosteroid Therapy

Cutaneous	Atrophy, striae, vascular effects, purpura, alopecia, pigmentation, acne, easy bruising
Cardiovascular	Hypertension, edema, atherosclerosis
Gastrointestinal	Nausea, vomiting, intestinal perforation, pancreatitis, esophagitis
Gynecological/obstetrical	Amenorrhea, gestational diabetes, adrenal suppression of infant
Neuropsychiatric	Psychosis, peripheral neuropathy, pseudotumor cerebri, depression/mood disorders, impaired cognitive function, seizures, insomnia, irritability
Metabolic	Hyperglycemia, hyperlipidemia, obesity, hypocalcemia, hypokalemia, buffalo hump
Musculoskeletal	Osteoporosis/osteopenia, aseptic necrosis, growth retardation, muscle atrophy, myopathy
Hematological	Leukocytosis, lymphopenia, eosinophenia, infection, immunosuppression, impaired fibroplasia, decreased mitotic rate
Ophthalmalogical	Cataracts, glaucoma, infection, exophthalmoses, hemorrhage
Endocrine	Hypothalamic-pituitary-adrenal axis suppression, hirsutism, moon facies
Pediatric	Growth retardation

Adapted from Yang and Lichtenstein[163] with permission.

hirsutism (7%), petechial bleeding (6%), and striae (6%). Prolonged corticosteroid therapy can result in multiple serious side effects including hypertension, new onset diabetes mellitus, infection, osteonecrosis, steroid associated osteoporosis, myopathy, psychosis, cataracts, and glaucoma.[65–67] Table 3 lists potential side effects of corticosteroid therapy.

For moderate to severe UC, the preferred initial prednisone dose is 40 mg/day administered as a single dose. The optimal tapering strategy has not been determined, but experienced clinicians will typically treat the patient with prednisone 40 mg/day for 2 to 4 weeks, then taper by 5 mg/week to a daily dose of 20 mg/day, then slow the taper to 2.5 mg/week until prednisone is discontinued. For severe UC, requiring hospitalization, hydrocortisone 300 to 400 mg/day or methylprednisolone 40 to 60 mg/day is used. Five to seven days are required prior to determining whether the patient has failed steroids.

ANTIBIOTICS

The lack of efficacy of antibiotics in the treatment of UC and Crohn's disease is somewhat surprising given the presumed role of bacteria in the etiology of IBD. One placebo-controlled trial of ciprofloxacin in moderately active UC showed benefit[68] while another was negative.[69] The addition of intravenous ciprofloxacin to steroids in severe UC was also not of benefit.[70] Oral tobramycin had short-term efficacy[71] in UC but could not maintain remission.[72] In acute severe UC, the combination of tobramycin and metronidazole,[73] oral vancomycin alone,[74] or intravenous metronidazole alone[75] were not of added benefit to corticosteroids. Finally, in a small placebo-controlled trial, rifaximin, a nonabsorbed, broad-spectrum antibiotic, was not statistically better than placebo in overall clinical outcome in patients with steroid-refractory severe UC, but did have a significant reduction in stool frequency, rectal bleeding, and sigmoidoscopic score compared with placebo.[76] Larger trials are underway.

Antibiotics should not be used without evidence of infection in patients with mild to moderate UC. Although evidence does not support their use in severe UC, in clinical practice the hospitalized patient may receive antibiotics as prophylaxis against bacterial translocation in the severely inflamed colon.

PROBIOTICS

Probiotics are live nonpathogenic organisms that confer health benefits by improving the microbial balance. While the formulation VSL3 has shown clear benefit for prevention of pouchitis after ileal-pouch surgery[77] and maintenance of remission in chronic pouchitis,[78] their benefit and that of other probiotics formulations in UC are still to be proven. Two small controlled studies have shown that *E. coli Nissle* is effective for maintenance of remission in UC.[79,80] An open label trial of VSL3 in mildly to moderately active UC demonstrated a remission rate of 63%. However, patients were on other agents such as mesalamine and steroids.[81] Larger controlled trials are needed to prove efficacy in both induction and maintenance of remission in UC.

NICOTINE

Nonsmokers and former smokers have higher rates of UC than current smokers.[3] Also, smokers with UC who stop smoking experience increased severity of disease.[82] The mechanism of this effect is thought to be due to nicotine, but is not completely elucidated.[83,84] Placebo-controlled trials of transdermal nicotine patches demonstrated efficacy in achieving clinical remission or improvement at doses of 25 mg/24 hours[85] and 22 mg/24 hours.[86] However, it was not effective for maintenance,[87] although an uncontrolled study suggested that patients who are treated with transdermal nicotine

maintain their response longer than those treated with corticosteroids.[88] Nicotine enemas also demonstrated benefit in uncontrolled trials.[89,90] The major drawback of nicotine use is the high percentage of side effects, especially in patients who have never smoked before. These side effects include skin irritation, lightheadedness, nausea, vomiting, diaphoresis, central nervous system disturbances, and insomnia.[84]

IMMUNOSUPPRESSANTS

While 5-ASA agents are the first line for induction and maintenance of remission in mild to moderate UC and steroids are used for induction of remission in moderate to severe UC, immune modifier drugs are used to induce remission in steroid-dependent or steroid-refractory disease, maintain remission in those patients for whom 5-ASA agents are inadequate, and as salvage therapy in severe disease refractory to steroid therapy.

Azathioprine/6-Mercaptopurine

6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA) are purine antimetabolite drugs demonstrated to be effective for the induction and maintenance of remission in UC and have proven steroid-sparing effects. The efficacy of 6-MP was recognized as early as 1962 in a case report by Bean.[91] Though some controlled studies of AZA versus placebo and AZA versus sulfasalazine in the treatment of acute attacks of colitis found no significant benefit,[89,92] others found that AZA use resulted in improved disease activity, a decreased need for steroids,[93] and prolonged rates of remission.[94] Multiple uncontrolled studies confirmed the benefits of AZA/6-MP.[95–99]

Effective doses of AZA are 2.0 to 3.0 mg/kg/day and of 6-MP are 1.0 to 1.5 mg/kg/day and may take up to 17 weeks to take complete effect.[100] Though some physicians begin at low doses and titrate upwards, our practice is to begin at full dose with careful monitoring of the compete blood count. There is no role for intravenous loading of AZA in severe UC.[101] Thiopurine S-methyltransferase (TPMT) phenotype or genotype can aid in determining safety and optimal dosage of AZA/6-MP. Low to intermediate levels of TPMT are associated with leukopenia in rheumatoid arthritis[102] and with Crohn's disease.[103] Based on these observations, it is recommended that patients with normal TPMT activity receive standard doses of AZA or 6-MP. Patients with intermediate activity should receive 50% of the standard dose and those who have no TPMT activity should not be treated with the drug.[104] The use of metabolite levels (6-TGN [thioguanine nucleotides] and 6-MMP [6-methylmercaptopurine]) to gauge optimal dosing of AZA/6-MP is controversial. Though two studies supported its use,[105,106] three others failed to demonstrate a consistent relationship between clinical efficacy and erythrocyte 6-TGN concentrations.[107–109]

Allergic reactions occur in 5% of patients taking AZA or 6-MP and include pancreatitis, fever, rash, malaise, nausea, diarrhea, and some cases of hepatitis.[110] Nonallergic reactions include bone marrow suppression leading to leukopenia, anemia or thrombocytopenia, opportunistic infection, and hepatitis. Lymphoma does not appear to be increased above what is expected in IBD,[110–112] though there may be an increase in Epstein-Barr virus-associated lymphomas in patients treated with AZA/6-MP.[113]

Methotrexate

Methotrexate (MTX) has demonstrated benefit for the induction and maintenance of remission in Crohn's disease[114,115]; however, its benefit in UC is not well established. Uncontrolled data have shown response in small series of patients with UC.[116–118] The only controlled trial in UC was by Oren and associates,[119] which compared oral MTX 12.5 mg/week with placebo in 67 patients with chronic active UC. No difference was found between the MTX and placebo group in remission and relapse rates. A recent study reported on patients with steroid-dependent or steroid-resistant active UC.[120] Ten patients were intolerant or resistant to AZA and were switched to MTX 12.5 mg IM/ week. Six of 10 (60%) achieved clinical remission, 40% achieved clinical response, and 20% subsequently relapsed. Available data suggest that AZA/6-MP should be the first choice for maintenance and steroid sparing in UC, but MTX can be tried in those who are intolerant or resistant to AZA/6-MP. Our usual starting dose is 25 mg SQ/week, though once remission is achieved, 15 mg SQ/week can be used for maintenance.

MTX should always be given with folic acid 1 mg per day. Use in patients who are diabetic, obese, use excessive alcohol, or have known liver abnormalities is contraindicated. MTX is teratogenic and should not be used in men or women attempting conception. Increased serum transaminases and hypersensitivity reactions such as rash and pneumonitis can sometimes be seen.

Cyclosporine

Cyclosporine (CSA) is a calcineurin inhibitor that is used as salvage therapy for induction of remission in severe, steroid-refractory UC that would otherwise require colectomy. There are four randomized trials that have demonstrated the efficacy of CSA in severe UC. The first, by Lichtiger et al, found that 9/11 (82%) steroid-refractory UC patients had clinical response with 4 mg/kg/day of CSA in combination with intravenous steroids, versus none of placebo-treated patients on intravenous steroids alone.[121] Two other controlled studies

suggested that CSA alone at a dose of 4 mg/kg/day without steroids is effective in inducing remission in severe UC.[122,123] Finally, a study by Van Assche and colleagues found that 2 mg/kg/day of CSA is equivalent to 4 mg/kg/day in achieving response in severe UC.[124]

Patients who respond to 4 mg/kg/day of IV CSA are continued on the drug for 7 to 10 days. The target whole blood CSA level is 300 to 350 ng/ml for the 4 mg/kg/day dose or 150 to 250 ng/ml for the 2 mg/kg/day dose. They are then converted to oral CSA at a dose of 8 mg/kg/day or twice the IV dose in hospital.[125] The desired CSA level on oral dose is 150 to 300 ng/ml. Unfortunately, 45% of patients on oral CSA alone will require colectomy at 6 months.[126] This can be decreased to 20% by the addition of 6-MP/AZA at discharge from the hospital.[126] Patients are also continued on prednisone, which is tapered during outpatient follow-up. This regimen of triple immunosuppressive therapy with CSA, 6-MP/AZA, and prednisone can lead to significant infectious complications. For this reason, trimethoprim/sulfamethoxazole is added for prophylaxis. One uncontrolled study suggested that patients responding to IV CSA can be started on oral AZA without oral CSA, and prednisone can be tapered accordingly[127]; however, the colectomy rate was 41%.

An oral, microemulsion form of CSA (Neoral) has been developed which has increased oral bioavailability and improved absorption from the small bowel.[128] The pharmokinetic parameters of CSA microemulsion in patients with IBD appear to be similar to those of healthy volunteers.[129] Three small series have described efficacy of oral microemulsion CSA in severe UC,[130–132] though larger controlled trials are needed.

In a report from Mount Sinai Hospital on 111 IBD patients treated with CSA, the most frequent adverse events were paresthesias (51%), hypertension (43%), hypertrichosis (27%), renal insufficiency (23%), infections (20%), gingival hyperplasia (4%), seizures (3%), death (2%), and anaphylaxis (1%).[133] In a similar report from the University of Chicago on 74 patients with IBD treated with CSA, 54% experienced adverse events including severe events such as *Pneumocystis carinii* pneumonia in two patients, abdominal abscess, grand mal seizure, mycotic aneurysm, and renal insufficiency.[126] Table 4 lists drug interactions of CSA and tacrolimus.

CSA in severe UC is definitely effective, but its side-effect profile and tangible long-term failure rate must be discussed in depth with the patient debating colectomy versus salvage medical therapy. Also, patients who are not tolerant of AZA/6-MP are not good candidates for CSA therapy, as CSA alone has a high colectomy rate over time. Side effects may be decreased by using lower doses of IV CSA at 2 mg/kg/day, using antibiotic prophylaxis, or avoiding triple therapy with oral CSA, AZA and prednisone.

Table 4 Potential Drug Interactions of Cyclosporine and Tacrolimus

Inhibition of cytochrome P450	Calcium channel blockers
Increased CSA levels	Bromocriptine
	Metoclopramide
	Imidazoles
	Macrolide antibiotics
	Methylprednisolone
	Protease inhibitors
	Grapefruit juice
Induction of cytochrome P450	Rifampin
Decrease cyclosporine levels	Phenobarbital
	Phenytoin
	Carbamazepine
	Reverse transcriptase inhibitors
	St. John's wort

Adapted from Kornbluth, et al[125] with permission.

Tacrolimus

Tacrolimus is a calcineurin inhibitor like CSA. Controlled trials in severe UC have not been conducted to date, but multiple case series suggest efficacy. The first study was by Bousvaros et al[134] and described a 69% clinical response rate in 13 patients with steroid-refractory UC. However, at 1 year, only 38% of patients avoided colectomy. Three case series note salvage therapy with tacrolimus in steroid-resistant or steroid-dependent UC[135,136] as well as in a patient with toxic megacolon.[137] One trial compared intravenous to oral tacrolimus in 38 patients with refractory UC.[138] Oral and IV dosing was equivalent. Eighteen of 38 patients (47%) improved within 14 days. Thirty-five of 38 patients (92%) avoided colectomy at 28 days, but at 2 years, the colectomy rate was 50%.

The dose of oral tacrolimus is 0.1 to 0.2 mg/kg/day given in divided doses twice daily. The serum trough levels are 4 to 6 ng/ml. Patients should be monitored closely for evidence of infections and trimethoprim/sulfamethoxazole prophylaxis should be used. Side effects include transient renal insufficiency, tremor, paresthesias, hyperkalemia, and hypertension.[135] These often resolve with lowering of the dose.

Infliximab

Infliximab is a chimeric monoclonal antibody to tumor necrosis factor-α (TNF), a key inflammatory cytokine. While infliximab has made a dramatic impact on the treatment of Crohn's disease,[139] its role in UC is not clear. Sands and associates reported 11 patients in a controlled trial of infliximab in severe, steroid-refractory UC.[140] Four of eight patients (50%) who received infliximab had a clinical response, although one subsequently

required colectomy. Two small case series report response in severe UC,[141,142] but a larger randomized controlled trial was negative.[143] In this latter trial, patients with severe, steroid-refractory UC were randomized to infliximab 5 mg/kg or placebo at weeks 0 and 2. After 6 weeks, remission was achieved in 8/22 infliximab patients and 6/20 placebo (not significant). A controlled trial of infliximab in nonsteroid-refractory patients[144] randomized patients to either infliximab 5 mg/kg at 0, 2, and 6 weeks or intravenous prednisolone at 1.5 mg/kg daily for 2 weeks followed by a taper. Five of 6 patients receiving infliximab and 6/7 patients receiving steroids had a response. The two agents appear to be equivalent in this small study.

Clinical experience and a placebo-controlled trial[143] suggest that infliximab is not effective in steroid-refractory UC. This is further supported by a retrospective analysis of 27 patients with active UC who received infliximab.[145] While 44% of all UC patients achieved remission and 22% had a partial response, steroid-refractory patients were less likely to respond when compared with steroid-responsive patients (33% vs 83%; $p = 0.026$). Infliximab should not be used in severe, steroid-refractory UC. Evidence for its use in steroid-responsive disease is anecdotal at best and controlled studies are needed.

EXPERIMENTAL AGENTS

Heparin

Thrombotic events associated with UC and histologic evidence of microvascular thrombosis on colon biopsy suggested that anticoagulation may be an effective therapy for UC.[146] Uncontrolled studies did find unfractionated heparin to be of benefit,[147,148] but small controlled studies comparing unfractionated heparin to corticosteroids had mixed results.[149,150] Larger, placebo-controlled trials of low-molecular-weight heparin in studies of 100 patients and 138 patients, respectively, found no significant benefit over placebo.[151,152] Heparin is not effective for the treatment of UC but does appear to be safe with no increased risk of gastrointestinal bleeding, should the need for anticoagulation for other reasons arise in these patients.

BIOLOGICS: CYTOKINES AND ANTIBODIES

Investigational agents with preliminary reports of efficacy include vepolimomab (monoclonal antibody [mAb] to vascular adhesion protein-1)[153]; interleukin-2 (IL-2) antagonists such as basiliximab, which may increase response to steroids in steroid-resistant UC[154]; anti-CD3 antibodies, such as visilizumab, which has shown preliminary efficacy in steroid-resistant UC[155]; antibody to $\alpha 4\beta 7$, such as MLN-02, which mediates recruitment of lymphocytes to the gut and demonstrated safety and efficacy in a controlled trial in patients with active UC[156]; and interferon-β, which showed some clinical response in patients with steroid-refractory UC in a phase II, placebo-controlled trial.[157] Multiple other agents exist, but for all new agents, while preliminary results are exciting, randomized controlled trials are needed before widespread use is initiated.

LEUKOCYTAPHERESIS

One novel technique for the treatment of severe UC is leuckocytapheresis. Based on the theory that inflammation and damage to the colonic mucosa are caused by products of activated granulocytes, monocytes, and macrophages, an extracorporeal leukocytapheresis column (LCAP) was developed to remove these cells from the peripheral circulation, with reported efficacy in UC.[158] A randomized controlled trial in 76 active UC patients reported that addition of LCAP to corticosteroids improved clinical response with a reduction in steroid dosage.[159] These results were corroborated by a recent randomized trial from the same group showing that LCAP was more effective than sham perfusion (80% vs 33%; $p < 0.05$) in eliciting clinical response in patients with active UC.[160]

ALGORITHM FOR THE TREATMENT OF ULCERATIVE COLITIS

Figure 1 outlines the algorithm for the treatment of a flare of UC. When a patient presents with a flare, the diagnosis should be confirmed and the severity of the disease established. Colonoscopy with biopsy to confirm the diagnosis of UC and establish the extent of the disease should be performed in all new and established cases. A small bowel follow-through should be performed once at some point in the disease course to rule out the diagnosis of Crohn's disease. Stool studies should be sent in all acute flares to rule out superinfection with *Clostridium difficile*, bacteria, or ova and parasites. In a patient with severe UC, an unprepped flexible sigmoidoscopy rather than full colonoscopy should be performed with biopsies of the rectum for histology and viral culture. This will confirm the severity of the disease and will also rule out cytomegalovirus (CMV). One study reported that 36% of patients with steroid-refractory colitis had CMV on rectal specimens.[161] The majority of these patients responded to antiviral therapy with foscarnet or ganciclovir. The severity of the disease can be determined by the Truelove and Witts score (Table 1).

For mild to moderate disease the first-line therapy is 5-ASA agents. If this is ineffective, steroids can be used to induce remission. If the patient cannot be tapered off the steroids or relapses after steroid withdrawal, immunosuppression with AZA/6-MP should be initiated for steroid-sparing and maintenance effects.

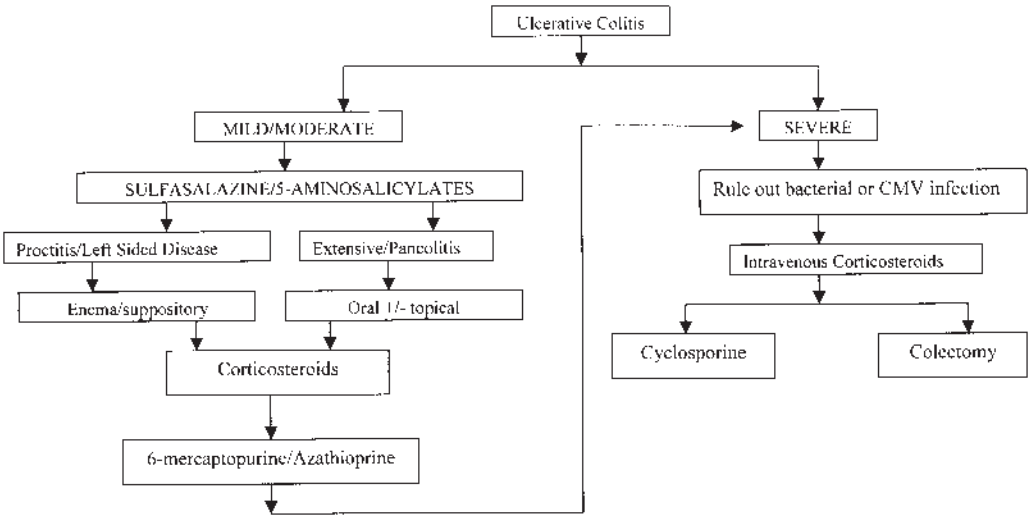

Figure 1 An algorithm for the medial management of mild, moderate, and severe ulcerative colitis. Progression along arrows is indicated if prior therapies fail.

In the patient with severe disease not responding to oral steroids, intravenous steroids are indicated in an inpatient setting. If there is no response after 5 to 7 days, CSA should be offered if the patient is an appropriate candidate. Patients who are intolerant of AZA/6-MP are not good candidates as colectomy rates are high in patients on CSA alone. Theoretically, MTX can be used instead, though its use in UC has less supportive evidence. Patient reluctance to use CSA or failure to respond to CSA would then lead to colectomy.

Aggressive medical therapy with immunosuppressants does not increase the risk of postoperative complications after colectomy and ileal pouch-anal anastomosis.[162] Factors that predicted an increase in short-term complications were high-dose steroids and severe disease. Variations on this algorithm with experimental or anecdotal agents can be tried as long as the patient is fully informed and the physician is comfortable with these drugs. However, larger controlled trials are needed before widespread use can be adopted.

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