Medical Treatment of Ulcerative Colitis

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Abstract
Ulcerative colitis is an inflammatory bowel disease of uncertain etiology with recurrent symptoms and considerable morbidity. There is no known medical cure for ulcerative colitis. The ultimate goal of treatment in any patient suffering from ulcerative colitis is inducing and maintaining clinical remission. New uses are being found for old drugs, and more and more new drugs are becoming available. This article is not only intended to help clinicians to evaluate new treatments for ulcerative colitis, but also to revisit older treatments with a critical eye.

INTRODUCTION
Ulcerative colitis is an idiopathic inflammatory bowel disease characterized by colonic mucosal inflammation and a chronic relapsing course. It affects about 11 in 100,000 persons in the United States. One house to house survey conducted in North India found the incidence of ulcerative colitis not much less than reported from the western world. The exact etiology of ulcerative colitis is not known, but it appears to be triggered by a dysregulated immune response, perhaps to a currently unknown pathogen. Patients with ulcerative colitis usually present with diarrhea, rectal bleeding, tenesmus, passing of mucus and abdominal pain. Diagnoses are made on the basis of clinical, endoscopic and histopathological findings. Usually, ulcerative colitis is mildly active, but it can be life-threatening – during severe attacks because of colonic and systemic complications. It is also well established that patients with long-term ulcerative colitis are at an increased risk of developing colorectal cancer.

Pharmacological Agents
Efforts at managing ulcerative colitis are directed at decreasing or eliminating mucosal inflammation and symptoms, thereby improving the patient’s quality of life. Accomplishing these goals requires careful selection of therapeutic agents based on symptom severity and drug side effects (Table 1). The therapeutic options vary depending upon the anatomic extent of the colonic involvement and clinical severity of an ulcerative colitis attack.

5-Aminosalicylic Acid Compounds
5-Aminosalicylic acid (5-ASA) compounds, also known as aminosalicylates are the cornerstone of medical therapy for active ulcerative colitis.

SULFASALAZINE
Sulfasalazine possesses both anti-inflammatory (5-ASA) and antibacterial (sulfapyridine) properties. Taken orally, the drug is delivered intact into the right colon and subsequently is degraded by coliform bacteria into 5-ASA, the active moiety and sulfapyridine, which helps transport 5-ASA to target areas. A major drawback to its use, however, is that the most effective doses also tend to be associated with intolerable toxicity; nearly one out of every three sulfasalazine-treated patients will develop adverse reactions. Common adverse effects include nausea, headache, vomiting, dyspepsia and anorexia, while less frequent, but more serious adverse effects include agranulocytosis, megaloblastic or hemolytic anemia, pancreatitis and sperm abnormalities. Patients with sulfa allergies should avoid sulfasalazine. Folic acid supplementation is recommended because sulfasalazine inhibits folate absorption.

NEWER AMINOSALICYLATES
Newer aminosalicylates deliver 5-ASA to the distal bowel without the sulfapyridine, thus allowing us to administer higher doses of the medication while limiting adverse effects and systemic toxicity. In equimolar doses, the oral 5-ASA preparations are equivalent in efficacy to sulfasalazine and their safety profile is similar or superior to that of placebo. Orally ingested 5-ASA alone undergoes rapid absorption in the jejunum and is therefore of limited efficacy in patients with colonic disease. Two main types of delayed release formulations have been developed to overcome this deficiency. The most commonly used aminosalicylate, is Meselamine, 5-ASA enveloped in a coating that dissolves at pH of 7 in the distal ileum and colon. The next preparation is a controlled release capsule which consists of 5-ASA encapsulated by ethylcellulose microgranules. This preparation will allow gradual release of 5-ASA from the jejunum to the colon. Rectal (topical) therapies are also available as mesalamine suppositories.
or enemas. The other two 5-ASA preparations which are available are Olsalazine and Balsalazide. The former consists of two 5-ASA molecules linked by a diazo bond and the latter consists of 5-ASA molecule linked by a diazo bond to an inert, unabsorbed carrier molecule. Both these formulations require colonic bacteria to break down the diazo bond and release 5-ASA moiety.\(^7,8\) Thus, they are also mainly active in the colon. The most recent advance in 5-ASA oral therapy includes recently FDA approved delayed and extended release formulation which is MMX mesalamine.\(^9\) This method employs a gastro-resistant polymer to delay release of the active drug until it reaches the terminal ileum and the MMX drug delivery technology is believed to extend delivery of 5-ASA consistently throughout the entire colon. The medication is prescribed as once a day dosage. Aminosalicylates are usually well tolerated, but can cause mild and transient side effects like headache and abdominal discomfort. Olsalazine causes watery diarrhea in about 10% of patients. Other side effects like pneumonitis, pericarditis, pancreatitis and thrombocytopenia are rare.

In last few years, several trials have demonstrated that 5-ASA therapy can prevent the development of dysplasia and cancer in patients with long standing ulcerative colitis.\(^10\) Educating patients about this potential benefit may increase their adherence to treatment.

**Corticosteroids**

Corticosteroids are potent, rapidly acting oral, rectal or parenteral agents used for acute treatment of patients with moderate to severe relapses of ulcerative colitis. They are potent anti-inflammatory agents acting through inhibition of several inflammatory pathways. The short-term side effects of steroids include acne, moon face, edema, mood disturbance, dyspepsia and glucose intolerance. The long-term side effects include cataracts, osteopenia/osteoporosis, osteonecrosis, myopathy and susceptibility to infection. Effects during withdrawal include adrenal insufficiency, a syndrome of myalgia and arthralgia or raised intracranial pressure. Complete steroid withdrawal is facilitated by early introduction of agents like Azathioprine (AZA) or timely surgery. Corticosteroid enemas are beneficial in patients with left-sided/distal ulcerative colitis.\(^11\) The foam preparation may facilitate retention and thus may be more effective than the liquid preparations. Some systemic absorption occurs, but serious side effects like adrenal suppression, etc. are uncommon. Budesonide is a poorly absorbed corticosteroid with limited bio-availability due to extensive first-past metabolism (degraded by the liver and red blood cells that can produce therapeutic benefit with reduced systemic side effects).\(^12\) It is designed to deliver steroids to the distal small bowel and proximal colon. The ileal-release preparations of budesonide are indicated for the treatment of patient’s with ileal and right-sided colonic Crohn’s disease.\(^13\) The efficacy of enterically coated budesonide in treatment of ulcerative colitis has not been established. However controlled trials have demonstrated that budesonide enemas are effective for inducing remission in left-sided ulcerative colitis.\(^14\)

**IMMUNOMODULATORS**

Azathioprine (AZA) and 6-Mercaptopurine (6-MP) are chemically related immunomodulators. AZA is nonenzymatically metabolized to 6-MP and subsequently to 6-thioguanine nucleotides. These drugs are useful for patients who are refractory to, or cannot be weaned from oral steroids. Although their slow onset of action (three to six months are required for optimization of benefit) may limit their utility in active therapy, AZA and 6-MP have each demonstrated efficacy in maintaining remission.\(^15,16\) Recent studies have shown that these immunosuppressive agents have a more favorable adverse effect profile than was originally believed. Fewer than 10% of patients stop therapy due to reversible bone marrow suppression and fewer than 3% develop pancreatitis or allergies characterized by abdominal pain, fever and rash. Pancreatitis is a contraindication to continued use of these drugs. One large retrospective review failed to find a significant association between Azathioprine and the development of lymphoma or leukemia.\(^17\) However one recent meta-analysis showed a significant increase in risk of lymphoma in inflammatory bowel disease patients treated with AZA or 6-MP.\(^18\) It is advisable to obtain a complete blood count every two weeks during the initial treatment phase and every three months for patients on maintenance treatment. It has been suggested that direct measurement of 6-MP metabolites like 6-thioguanine (6-TG) and 6-Methylmercaptopurine (6-MMP) could be useful for optimizing the efficacy and minimizing the toxicity related to 6-MP.
While Methotrexate has been found effective for inducing remission or preventing relapse in Crohn’s disease, no comparable trials have addressed the role of methotrexate in induction or maintenance of remission in ulcerative colitis.  

**INFLEXIMAB**

Infliximab is a chimeric anti-tumour necrosis factor alpha monoclonal antibody with potent anti-inflammatory effects and is classified as one of the biological agents for treatment of ulcerative colitis. Tumor necrosis factor (TNF) has a central role in the pathogenesis of mucosal inflammation in Crohn’s disease. The efficacy in Crohn’s disease provided the rationale for clinical trials of infliximab and other anti-TNF agents in patients with ulcerative colitis. Two recent randomized, double blind, placebo controlled trials (ACT 1 and ACT 2) demonstrated efficacy of infliximab in the induction and maintenance of mild to moderate ulcerative colitis.  

USFDA recently approved the use of this drug to treat patients with moderate to severe ulcerative colitis who have not completely responded to other treatments. The medication is administered intravenously at the dose of 5 mg/kg at 0, 2 and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter. Because infliximab is associated with four or five fold increase in risk of tuberculosis, all patients should have chest x-ray to exclude past or present infection. Infusion reactions are rare and usually respond to slowing the infusion rate or treatment with antihistaminics and sometimes corticosteroids. Anaphylactic reactions have been reported. A delayed reaction consisting of myalgia, fever and joint pain may occur if there has been an interval of more than one year following a previous infusion. The formation of antibodies to infliximab may also be a problem and has been associated with reduced efficacy and infusion reactions. This can be avoided by using this medication at recommended regular intervals. The use of immunomodulators (like AZA and 6-MP) is also reported to reduce development of antibodies to infliximab and some authorities recommend starting one of the immune modulators before the patient is put on infliximab. Long-term data on use of infliximab in ulcerative colitis is not yet available and at this time it is best considered for patients with acute steroid refractory disease who are reluctant to undergo colectomy.

**CYCLOSPORINE**

Cyclosporine is a potent immunosuppressive which has a rapid onset of action (more rapid than AZA or 6-MP). Many open studies confirm that intravenous cyclosporine in a short-term data, at a dose of 2-4 mg/kg per day induces clinical improvement in more than 75% of the patients suffering from severe ulcerative colitis. Intravenous cyclosporine often demonstrates clinical efficacy within one week of the onset of treatment. Oral maintenance with cyclosporine is not very popular because of its toxicity and long-term failure rate. One of the immunomodulators (AZA or 6-MP) is usually started concurrently with initiation of treatment with cyclosporine with the hope that AZA or 6-MP will be effective within three to six months and hence cyclosporine is rarely continued for more than 3-6 months. Measurement of blood pressure, full blood count, renal function and cyclosporine serum levels are advisable at 0, 1 and 2 weeks and then every month. Measurement of serum cholesterol and magnesium are appropriate before starting therapy because the risk of convulsions increases in patients with low cholesterol or magnesium. The other minor side effects include tremor, paresthesia, malaise, headache and abnormal liver functions. Major complications include renal impairment and infections. Prophylaxis against Pneumocystis carinii pneumonia is advised in all patients on cyclosporine. Cyclosporine enemas are not effective in left-sided ulcerative colitis.

**Other Experimental Approaches**

Probiotics, as well as oral antibiotics have not shown any efficacy in the treatment of active ulcerative colitis. The use of fish oil showed some promising results; however, the lack of long-term effectiveness, bad taste, and the dosage requiring 15-18 capsules per day make this medicine not actively being used in clinical settings. Several epidemiologic studies have suggested a protective effect of cigarette smoking on the activity of ulcerative colitis. While two placebo control trials of use of nicotine patch in mild active ulcerative colitis showed a beneficial effect of nicotine therapy, the same therapy has not been found to be effective in maintaining the remission. Interesting case reports showing unexpected benefit in the activity of colitis with the use of heparin suggested initiation of a few placebo control trials using subcutaneous or intravenous heparin. The overall results were negative.

**Therapy**

Ulcerative colitis is usually classified into severity in two different ways. The first one is according to the extent of involvement. The second one is according to the symptoms. By definition, the rectum is involved in at least 95% of the patients suffering from ulcerative colitis. If the disease is limited only to the rectum, it is known as proctitis; proctosigmoiditis refers to disease limited to the rectum and sigmoid colon and left-sided ulcerative colitis involves the descending colon, sigmoid colon, and rectum. When the term pancolitis is used, it suggests involvement of the whole colon or most of the colon. In the past, the severity of disease was determined clinically into categories of mild disease, severe disease, and fulminant disease. However, in the present era of colonoscopy based diagnosis and follow up, it is easy to manage these patients according to the anatomically defined severity (Table 2). If you take a generalized approach, the extent of colonic involvement usually collaborates with the severity of clinical symptoms.

**TREATMENT OF PROCTITIS**

For the patient whose disease is limited to the last 10-12 cm of the rectum, it is usual practice to begin treatment...
using 1,000 mg. 5-ASA suppository once a day or a steroid suppository which is recommended twice a day. Suppositories are never effective for the disease beyond upper rectum (about 15-20 cm above the anal verge) and in such situations the treatment described below for proctosigmoiditis and left-sided colitis should be followed. For maintenance of remission, long-term treatment using 5-ASA suppositories should be carried out. Less than once a day maintenance therapy (such as every other day) is not recommended. If the symptoms are not controlled, the alternatives are 5-ASA enema or hydrocortisone foam or enema. In the rare situation when the patient is not willing to try any of these local therapies, he can receive oral 5-ASA preparation.

**TREATMENT OF PROCTOSIGMOIDITIS AND LEFT-SIDED COLITIS**

Topical (rectal) treatments like 5-ASA enemas are superior to oral preparations in the treatment and maintenance of remission of proctosigmoiditis and left-sided colitis. Topical corticosteroid enemas or foams are effective as active therapy, but not in remission. The topical therapy generally has a quicker response time and a less frequent dosing schedule. Meta-analysis has clearly demonstrated that 5-ASA enema is superior to topical corticosteroids in the management of distal ulcerative colitis. For proctosigmoiditis, the standard recommendation is to begin treatment with 4 gm 5-ASA enema every night. The response is usually seen within four to six weeks. If the patient does not respond, additional morning 5-ASA or hydrocortisone enema can be considered. Once the patient goes into remission, frequency of enema should be tapered to every night or even on alternate nights. For patients who do not respond to or tolerate rectal preparation, an oral 5-ASA medication should be used. Combination therapy consisting of rectal, as well as oral 5-ASA preparation has been found to be more effective than either alone. Oral therapy with sulfasalazine, mesalamine, olsalazine or balsalazide is beneficial in achieving and maintaining the remission. These drugs are maximally effective within four weeks of initiation of treatment and are effective in more than two-thirds of the patients. The equivalent doses of these preparations are mentioned in the Table 1. In case of an inadequate response, the drug should be raised to its maximum therapeutic dosage. Thus mesalamine can be given up to 4.8 gm a day. Oral corticosteroids are typically reserved for patients who do not respond to oral 5-ASA agents with or without rectal agents or for patients who need rapid improvement. The starting dose of Prednisone is usually 40-60 mg a day depending on the severity of symptoms and weight of the patient. This dose is generally effective within two weeks and should be then tapered, usually by 5 mg per week. As mentioned before, there is no scientific evidence to support use of chronic steroid therapy in maintaining the remission and the longer the patient gets these preparations, the more significant the toxicities are. For small numbers of steroid refractory and/or steroid dependent patients with left-sided colitis, azathioprine or 6-MP should be considered if symptoms of disease continue despite use of steroids for six months. Control trials have shown that Budesonide enemas are effective for inducing remission in left-sided ulcerative colitis. The efficacy of this drug was comparable to conventional corticosteroids. But 5-ASA enemas were significantly better than conventional rectal steroids and hence it is recommended that budesonide enemas should generally be reserved for patients who failed 5-ASA enemas.

**PANCOLITIS (EXTENSIVE COLITIS)**

Topical therapy alone is not adequate in achieving remission when the disease extends proximal to the splenic flexure. Therefore, oral mesalamine is preferred for treatment of mild to moderate colitis extending proximal to the splenic flexure both for active disease and for maintenance of remission. Nevertheless, topical therapy is a useful adjunct to oral mesalamine in extensive colitis. Those who demonstrate severe disease or those who fail to respond to oral as well as rectal 5-ASA therapy should be started on oral Prednisone (40-60 mg a day). The dose of oral sulfasalazine should be titrated up to 4-6 gm per day or alternatively meselamine in the dose up to 4.8 gm per day. Responses are dose related. Up to 80% of the patients who receive daily doses of 4-6 gm of sulfasalazine or equivalent aminosalicylate manifest complete clinical remission or significant improvement in four weeks and approximately half achieve sigmoidoscopic remission. Azathioprine or 6-MP should be considered in patients in this category who are refractory to maximal doses of 5-ASA medications and require corticosteroids to control the symptoms. These drugs are not good options for patients who are unlikely to

**Table 2 : Options for inducing remission**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proctitis</th>
<th>Left sided colitis</th>
<th>Pancolitis</th>
<th>Severe fulminant colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rectal 5-ASA</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Oral 5-ASA or Sulfasalazine</td>
<td>X (rare)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3. Combination of 1 and 2</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Rectal Steroids</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Oral Steroids</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6. IV Steroids</td>
<td></td>
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<tr>
<td>7. IV Infliximab</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>8. IV Cyclosporine</td>
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comply with regular monitoring, and are unwilling to accept the risk of toxicity or have dysplasia or other indications for colectomy. The use of infliximab is recommended for severe ulcerative colitis, especially when it is steroid refractory in a patient who is reluctant to undergo colectomy and in whom cyclosporine is contraindicated. If the patient improves, the maintenance regimen should consist of sulfasalazine or one of the newer aminosalicylate preparation. As a rule, patients should not be treated chronically with steroids. Azathioprine or 6-MP may be useful as steroid sparing agents for steroid dependent agents and for maintenance of remission not adequately sustained by aminosalicylates, and occasionally for patients who are steroid-refractory, but no acutely ill. In patients whom remission was achieved with Azathioprine, continuation of the active drug reduced the twelve month relapse rate to 36%, compared to 59% on placebo.

**SEVERE OR FULMINANT COLITIS**

Patients who have failed to respond to maximum oral treatment with combination of 5-ASA preparation and steroids with or without topical therapy or those presenting with symptoms of severe disease (bloody stools up to 10-15 per day, fever, abdominal pain, dehydration and anemia) should be admitted for intensive intravenous therapy and monitoring. Close liaison with a surgeon should be maintained. The mainstay of therapy at this point is an intravenous steroid in a daily dose equivalent to 400 mg of hydrocortisone or 60 mg of methylprednisolone. Broad spectrum intravenous antibiotic may be added with signs of toxicity or with worsening symptoms despite maximal medical therapy. Studies have not demonstrated clinical benefit of an oral or rectal aminosalicylate so it is generally withheld. Patients who have severe colitis and/or megacolon with toxic signs (fever, leukocytosis, or worsening of symptoms) and who do not improve significantly within seven days of maximal medical therapy are unlikely to benefit from prolongation of a medical regimen and should either be referred for colectomy or offered treatment with intravenous cyclosporine. For patients responding to cyclosporine, the medication should be switched to oral preparation (8 mg/kg per day) and should be continued for three to four months. At the same time, azathioprine or 6-MP should be introduced. A recent randomized double blind trial comparing infliximab with placebo for rescue therapy in severe to moderately severe ulcerative colitis showed significant benefit for the patients on infliximab. Infliximab may turn out to be a good alternative to cyclosporine which has significant side effects and requires very close monitoring. To date no large clinical trial comparing cyclosporine with infliximab has been reported.

**Indications for Surgery**

Urgent surgery is needed for severe colitis not responding to five to seven days of adequate medical treatment and for toxic megacolon after 48-72 hours of ineffective treatment. Emergency surgery is mandatory for any perforation, massive hemorrhage or development of multiorgan failure.

**CONCLUSION**

The goal of therapy in inflammatory bowel disease is to induce and maintain remission in order to realize the best quality of life. In ulcerative colitis disease activity is almost always associated with presence of diarrhea or bloody stool and can be easily assessed by sigmoidoscopy. The principal goals of maintenance therapy are avoiding disease progression and relapse and obviating corticosteroids and surgery. Consistent adherence to the maintenance therapy is very important and should be emphasized at each follow up consult. Ulcerative colitis is often a lifelong, multifaceted disorder that extends beyond disease related symptoms. The medical management of ulcerative colitis is a constantly moving field and recent evolutions will undoubtedly change clinical practice in years to come.

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**REFERENCES**


