Induction of Remission with 5-Aminosalicylic Agents for Ulcerative Colitis Patients

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Ulcerative Colitis: Epidemiology, diagnosis, and disease severity

Incident cases of ulcerative colitis (UC) are concentrated in North America (especially, Canada) and Europe (especially, Scandinavia).

While incidence rates have been stable in recent years, developing countries and regions closer to the equator seem to have lower rates of disease. While not proved, poor sanitation (the hygiene hypothesis) and vitamin D levels may be protective against developing UC. Many studies have shown that cigarette smoking or appendectomy is protective against developing the disease. Genetic abnormalities are likely to be factors in developing ulcerative colitis since susceptibility genes have been identified, and monozygotic twins (14-19%) are much more concordant for the disease than are dizygotic twins (0-7%).

The typical presentation of patients with ulcerative colitis is diarrhea and rectal bleeding, although patients with ulcerative proctitis may have formed stools. Confirmation of the diagnosis requires negative stool cultures, and endoscopy and histology that are compatible with the diagnosis. Typical endoscopic findings of UC include: superficial ulcers, granularity, and mucosal friability.

The ACG Clinical Practice Guidelines have suggested the following criteria for disease severity in ulcerative colitis patients (2):

- Mild disease: < 4 stools/day, small amount of blood, normal ESR, no signs of toxicity
- Moderate disease: >4 stools/day, minimal signs of toxicity
- Severe disease: >6 stools per day, fever, tachycardia, anemia, elevated ESR
- Fulminant disease: >10 stools/day, continuous bleeding, toxicity, abdominal tenderness and distension, transfusion requirement, colonic dilation.

On presentation, more than 70% of patients will have moderately active
disease with only 20% having mildly active disease and the remainder having severely active for fulminant disease.8 About half of patients on presentation will have proctitis or proctosigmoiditis, 30% will have left sided disease, and the remainder will have pancolitis, defined as disease extending proximal to the splenic flexure, Figure 3.2,9 Previous reports of a more benign clinical course for patients with proctitis and left sided colitis (with only 15% exhibiting proximal extension of disease), have been recently questioned.10

The 5-Aminosalicylic acid agents

Since the 1940’s, when sulfasalazine was introduced, 5-aminosalicylic acid (5-ASA) agents have been the mainstay of therapy for ulcerative colitis patients. There are multiple mechanisms of action of this class of drugs including inhibition of arachidonic acid metabolism (both cyclo-oxygenase and lipoxygenase pathways), free radical scavenging, and peroxisome proliferator-activator receptor-γ activation. 5-ASA agents can be delivered topically also. All of the agents, except sulfasalazine are sulfa-free. The delivery system for 5-ASA of each preparation varies and may determine the site in the gastrointestinal tract where 5-ASA is released. For example, preparations with a diazo bond required colonic bacteria to cleave that diazo bond, and therefore are most effective in the large bowel. The following is a list of the 5-ASA preparations available in the U.S and Figure 4 illustrates the location(s) of oral mesalamine release in the gastrointestinal tract.

- Sulfasalazine – diazo bond with sulfapyradine, colonic release
- Olsalazine (Dipentum®) - diazo bond of two 5-ASAs, colonic release
- Pentasa® - ethylcellulose/5-ASA beads, small bowel and colonic release
- Asacol® - Eudragit-S coating that releases at pH7, ileocolonic release
- Colazal® - diazo bond to inert polymer, colonic release
- Lialda® - Eudragit-S coating of metallomatrix 5-ASA, ileocolonic release
- Apriso® - Eudragit-L (pH6) coating of 5-ASA-polymer coated beads, small bowel and colonic release
- Asacol-HD® - Eudragit-S and Eudragit-L coating, ileocolonic release
- Canasa® suppositories – topical rectal release
- Rowasa® enemas – topical rectosigmoid release

Induction of remission for mildly to moderately active disease

Even when given orally, 5-ASA acts topically. The carrier molecule (i.e. sulfapyridine in the case of sulfasalazine) or the protective coating protects 5-ASA from proximal absorption in the gastrointestinal tract so it can act topically in the affected colon. In patients with mildly to moderately active disease, giving the combination of oral and topical 5-ASA is more effective than either one individually.11 Apparently, controlling the rectal inflammation with topical 5-ASA will decrease urgency, bleeding, and diarrhea even in patients with pancolitis.

The most recent studies of the oral 5-ASA agents all showed effectiveness against placebo. The ASCEND I, II, and III studies randomized ulcerative colitis patients to either Asacol® 2.4g daily or Asacol-HD® 4.8g daily for 6 weeks.12,13 There was no difference between regimens in patients with mildly active disease, but there were significant differences in patients with moderately active disease, with the higher 5-ASA dose being more effective. It was suggested that patients with mildly active disease be given 2.4g daily of Asacol® and patients with moderately active disease be given 4.8g of either Asacol® or Asacol-HD®.
Lialda®, a once-daily 5-ASA product, was tested in a randomized clinical trial of 2.4g, 4.8g, and placebo for 8 weeks. Remission rates with both Lialda® doses were significantly different from placebo, but not different from each other. Stool frequency, rectal bleeding, and mucosal healing rates were all significantly improved with Lialda®. Mucosal healing is believed to be a sign of sustained response to medication.

In a dose-finding study of Apriso®, 321 patients with active disease were randomized to 1.5g, 3g, or 4.5g daily. There were no significant differences in remission rates, time to response, endoscopic improvement or histologic improvement. Apparently, Apriso® at 1.5g daily is as effective as other preparations with higher 5-ASA content. In another study of Apriso® for induction therapy, 3g once daily dosing was as effective as 1g three times daily dosing, implying that once-daily dosing of Apriso® is efficacious. Of course, patients overwhelmingly prefer once-daily dosing.

**Induction of remission for severely active disease**

Patients with severely active disease have failed 5-ASA therapy and have failed oral steroids. Most of these patients need to be admitted to the hospital for intravenous steroids, which often is very helpful, induces remission, and allows patients to be followed on tapering doses of oral steroids and 5-ASA therapy. However, if intravenous steroids are unhelpful, then three options need to be discussed with the patient in detail.

- Infliximab 5mg/kg IV at weeks 0, 2, and 6, followed by an infusion every 8 weeks and with 5-ASA, tapering doses of steroids, and an immunosuppressive.
- Cyclosporine 2mg/kg IV daily for a maximum of 7 days, followed by oral cyclosporine for about 6 months, 5-ASA, tapering doses of steroids, and an immunosuppressive,
- Total proctocolectomy with ileal pouch-anal anastomosis, usually a 3-stage procedure.

If cyclosporine or infliximab is not effective within seven to 14 days, then surgery should be more strongly considered.

Patients with fulminant colitis or toxic megacolon should be considered for immediate surgery before IV steroids are administered. Up to 10% of these patients will have an unrecognized perforation at the time of surgery.

**Conclusions:**

Once the diagnosis of ulcerative colitis is made, patients should be immediately started on 5-ASA agents, both oral and topical. Patients with moderately active disease will require a higher dose of 5-ASA than patients with mildly active disease. There are many 5-ASA agents to choose from, and without unbiased head-to-head comparisons there is no preferred agent. For patients with severely active disease not responsive to IV steroids and who want to delay surgery, cyclosporine or infliximab are the best medical options.

**References:**


