Mild-Moderate Disease: Fine Tuning 5-ASA Drugs
In the last several years, there have been several modifications for the use of mesalamine agents for mild-moderate UC. pH-dependent mesalamine (Asacol®, Warner-Chilcott Pharmaceuticals) in an 800 mg tablet, in a dose of 4.8 gram daily demonstrated non-inferiority to 2.4 gram daily for induction of remission in patients with moderate disease. However, in a post hoc analysis, subsets of patients with prior use of topical agents, multiple oral drugs, or steroids fared somewhat better with the use of 4.8 gram daily, compared with 2.4 gram daily.

Earlier this year, the FDA granted approval for the use of once daily dosing of MMX-release mesalamine (Lialda®, Shire Pharmaceuticals) in a dose of 2.4 grams daily for maintenance of remission. Previously, the FDA approved granulated mesalamine in a dose of 1.5 grams (Apriso®, Salix Pharmaceuticals) for once daily dosing for maintenance of remission. It is important to recognize that not only for distal disease, but for more extensive disease as well, the combination of a topical 5-ASA with an oral 5-ASA drug, is more effective than either one alone.2,3

Infliximab (IFX) for Moderate-severe UC: Traditional Use, Additional Uses, and Unknown Uses
Undoubtedly, the most significant advance in the treatment of patients with UC, as for patients with Crohn’s disease, has been the introduction of infliximab for moderate-severe disease, as well as for its use in patients failing an intravenous course of steroids as inpatients. Infliximab in a dose of 5 mg/kg in an induction regimen at weeks 0, 2 and 6 is effective in achieving clinical response, remission and mucosal healing at week 8, and a maintenance dose of infliximab 5 mg/g infused every 8 weeks is effective to week 54.4

PPD testing should be performed prior to initiating treatment with infliximab. In those patients previously treated with BCG, or in those patients who may be anergic due to disease activity or secondary to immunosuppression, measurement of the gamma interferon release assay (Quantaferon gold), a serum measurement for TB antigen, may be helpful. In addition, prior to initiating treatment with an anti-TNF agent, there should be testing for hepatitis B antigen; seropositivity for hepatitis B mandates anti-viral treatment prior to initiating anti-TNF treatment. Additional recommendations regarding immunizations are covered in a following lecture during this session.

Patients who have an initial response to infliximab but in whom the response gradually wanes, i.e., a secondary loss of response, should have the dose increased to 10 mg/kg, and if the benefit is not sustained, should have the dosing interval shortened. The use of serum infliximab and antibody to infliximab (ATI) measurements may allow better guidance re: dose and interval changes. If serum levels are low in the presence of high antibody titers, it is unlikely that further dose increases may be of benefit. If, on the other hand, infliximab levels are low and ATI is absent, dose escalation and shortening of dose intervals are more likely to be of benefit.5 However, the time point at which to measure drug levels and ATI, and the absolute titers of each to guide dosing, has not been studied in a prospective controlled fashion, although serum trough levels of infliximab appear to be a useful predictor of infliximab response.6

Infliximab is also effective in the management of the inpatient with severe UC failing a 3-5 day course of IV steroids. In a double-blind RCT, the colectomy rate at 90 days after a single dose of infliximab 5mg/kg was 29% compared with 67% with placebo.7 In those patients with colectomy avoidance at day 90, 76% remained colectomy-free at two years compared with 46% of placebo-treated patients who had avoided colectomy at 90 days. In a retrospective review of 30 steroid refractory UC patients treated with infliximab, 53% required colectomy after a mean of 140 days.8

There are a number of unanswered questions regarding the optimal use of infliximab in UC. First, it is unknown whether the benefit of infliximab is enhanced by the addition of azathioprine, as it is in patients with Crohn’s disease naïve to both agents.9 At the time of this writing, adalimumab, which met its primary endpoint as induction of remission in UC, is undergoing FDA review for its approval in patients with UC.10 Its benefit in patients who have had a secondary loss of response, or who develop intolerance to infliximab, is unknown at present. Lastly, it is unknown whether infliximab can be discontinued with maintenance of its benefit after some period of time in patients with UC.

A prospective controlled trial (not published in full manuscript form at the time of this writing) compared infliximab to intravenous cyclosporine in patients refractory to a course of at least three days of IV steroids. There were no differences in colectomy avoidance at day seven or at the end of 98 days.11
Whatever the choice of first salvage drug in the patient failing a course of IV steroids, it is critical to recognize that resorting to the use of the alternative salvage drug within 30 days of failure of the first, results in only approximately a 30-40% steroid-free remission rate at one year, and that this approach has been associated with an approximately 20% serious infection rate and a 2% fatality rate.\(^{12,13}\)

### The increasing problem of Clostridium difficile (C. difficile)

The frequency of superimposed infection Clostridium difficile has increased dramatically in patients with UC as it has in the general population; especially worrisome is that the incidence of C. difficile in hospitalized patients with UC is rising dramatically as well. This infection results in higher costs, longer length of stay, and increased morbidity and mortality and it is more refractory to treatment in patients on immunosuppressive drugs.\(^{14,15}\) The high false negative rate of detection of C. difficile should improve as the PCR assay for C. difficile becomes more widely commercially available.

A recent prospective study of hospitalized patients (without IBD) demonstrated a high failure rate with metronidazole treatment for C. difficile in patients who had been recently treated with cephalosporins, in those who were C. difficile positive on admission, and in those transferred from another hospital. In such cases, therefore, vancomycin should be considered as the preferred initial antibiotic.\(^{16}\)

### Issues in Dysplasia Detection and Management

In an effort to increase the sensitivity of detecting dysplasia colonoscopically, several enhanced colonoscopic surveillance techniques have been studied. These methods aim to increase the recognition of nearly flat or minimally raised lesions and their associated mucosal pit patterns using mucosal dye spraying with either carmine indigo or methylene blue. Two series utilizing chromoendoscopy with standard white light microscopy with standard colonoscopes without magnification demonstrated a higher yield per biopsy and per patient in detecting dysplasia.\(^{17,18}\) However, the natural history of dysplastic lesions found by chromoendoscopy and not seen with routine white light colonoscopy is unknown.

At present, therefore, the recommendation to routinely utilize chromoendoscopy-enhanced surveillance in low risk patients awaits additional information regarding longer term follow-up. Given the increased yield of chromoendoscopy though, it may be of value in follow-up of the “higher risk” patient (i.e., patients with indefinite or known dysplasia not proceeding to colectomy), and to ensure adequacy of prior resection of polypoid or minimally-raised lesions. In any event, appropriate use of chromoendoscopy will require adequate training in the techniques of endoscopic staining and interpretation of mucosal pit patterns.

A number of series have addressed an approach to management of patients with longstanding UC who are found to have a polypoid or adenomatous mass within a colitic area.\(^{19-21}\) If the lesion is resected in its entirety by colonoscopic polypectomy and if no dysplasia is found in the adjacent flat mucosa or anywhere else in the colon, long term follow-up has not found an increased risk of cancer in these cases, suggesting that vigilant follow-up surveillance colonoscopy may suffice. Polyps with a plaque or carpet-like morphology that could not be endoscopically resected in their entirety were excluded from these studies; such cases should be referred for surgery. From a practical perspective, therefore, it matters little whether a mass lesion is called an adenoma-like mass (ALM), or a dysplasia-associated lesion or mass (DALM); the important issue is to determine whether or not the lesion is completely resectable endoscopically and the rest of the colon is free of dysplasia.

### References


