Maintenance of Remission with 5-Aminosalicylic Acid Agents for Ulcerative Colitis Patients

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The natural history of ulcerative colitis

Ulcerative colitis is a remitting and recurring disease. 5-Aminosalicylic acid (5-ASA) has been known for many years to maintain remission longer than in those not on 5-ASA, and to blunt the severity of the flares when they occur. While the early 5-ASA maintenance studies were carried out for 12 months, it is generally assumed that patients should be on maintenance therapy for an indefinite period of time, usually a lifetime.

One of the most serious complications of ulcerative colitis is the development of colorectal cancer. Lifetime risks are believed to be approximately 15%, but some have claimed that the risk can be as high as 30%. Risk factors for cancer include pancolitis, long duration of disease, chronically active disease, young age at symptom onset, and primary sclerosing cholangitis. Patients are encouraged to have cancer surveillance colonoscopy every 2-3 years and have surgery if definite dysplasia is found on biopsies. If 5-ASA agents are effective in reducing cancer risk, then surveillance examinations can be done less often than it is currently done, and be just as effective.

Using newer 5-ASA agents for maintenance of remission

Within the last two years, three new 5-ASA agents have been introduced into the market, Lialda®, Apriso®, and Asacol-HD® (*Table 1*). Only Apriso® is indicated for maintenance, and only Lialda® and Apriso® are indicated for once-daily dosing. However, in clinical practice it is highly likely that all three will be used for maintenance therapy with once daily-dosing.

In a study using Lialda® for maintenance therapy, 459 patients with ulcerative colitis in remission were randomized to receive 2.4g once-daily or 1.2g twice-daily for 12 months. By the end of the study, there was no significant difference in clinical remission (89% with once-daily vs. 93% with twice-daily), or clinical and endoscopic remission (64% vs. 68%). Serious adverse events were rare in both groups and mostly related to ulcerative colitis exacerbation.

Two maintenance studies on Apriso® have been performed. In a randomized clinical trial of 300 ulcerative colitis patients in remission, Apriso® 1.5g daily was compared to placebo over a 6 month period. Remission rates at the end of the study were 79% in the Apriso® group and 58% in placebo (P<0.001). In another randomized clinical trial, 487 patients with ulcerative colitis in remission and on another 5-ASA agent were randomized to Apriso® 1.5g daily or placebo for 6 months. Once again, 6-month remission rates were significantly different between groups (78% v. 59%, P<0.001). In both trials, there were no differences in serious adverse events between groups.
In the largest randomized clinical trial done in IBD patients, 1027 ulcerative colitis patients in remission and on Asacol® were randomized to receive that same Asacol® dose (1.6g to 2.4g) with either once-daily or twice-daily dosing for 12 months. By the end of the study, 85% of each group was still in remission. The times to relapse and the rate of serious adverse events were similar between groups.

The choice of maintenance 5-ASA medication for ulcerative colitis patients is not always clear. Patients often prefer to take the same medication that induced the remission, which is not an unreasonable consideration. However, as will be discussed later, adherence to maintenance 5-ASA medication is a major concern for ulcerative colitis patients. The once-daily 5-ASA agents are associated with better adherence, and since they appear to be safe and effective, they should be preferentially offered to patients. Cost comparisons among Apriso®, Lialda®, and Asacol-HD® vary on the amount of 5-ASA being prescribed, different insurance plans, and manufacturer discounts. Since Apriso® is effective with less 5-ASA use (1.5g as opposed to 2.4g), there is usually a cost advantage with Apriso® (Table 1).

**5-ASA for colorectal cancer chemoprevention**

5-ASA has been studied as a possible colorectal cancer chemopreventive agent. Possible mechanisms for this effect include:

- Inhibition of cyclo-oxygenase activity
- Inactivation of reactive oxygen species (free radicals)
- Increase in apoptosis through NF-κB suppression
- Decrease in IL-2 production which decreases clonal proliferation of T-cells
- Activation of peroxisome proliferator-activator receptor-γ which is an epithelial cell anti-proliferative agent.

The epidemiologic studies that have been performed examining 5-ASA as a cancer chemopreventive agent have been equivocal. However, a meta-analysis that included 9 case-control or cohort studies, found that the common odds ratio for 5-ASA’s association with colorectal cancer was 0.51 (95% confidence interval 0.29-0.92), meaning that long-term 5-ASA use could decrease colorectal cancer risk by as much as 50% (Figure 1). This risk reduction is substantial, but only means that cancer surveillance colonoscopy can be done less often, not eliminated. Since adherence to 5-ASA medication is a problem for ulcerative colitis patients, both the disease maintenance effect and the cancer chemopreventive effect should be emphasized.

![Figure 1: Meta-analysis of the epidemiologic studies linking 5-ASA use to prevention of colorectal cancer or dysplasia (reference 7)](image-url)
Adherence to therapy

Adherence to maintenance 5-ASA is a particularly important problem for ulcerative colitis patients. Fully 60% of patients do not take the prescribed medications\textsuperscript{8,9}. Some important factors found to be important for non-adherence include:

- Male gender
- Single status
- Not able to appreciate need for medications when in remission
- Cost
- Complicated dosing regimen
- Fear of side effects
- Large number of tablets.

Forgetfulness is the most important reason that patients cite for non-adherence, but it is much easier to forget medication when there is a multiple daily dose regimen.

Importantly, maintenance is effective when patients are adherent to medication. In a cohort study of 5-ASA use for ulcerative colitis patients in remission, 89% of those who were adherent to medication were still in remission after 30 months, compared to just 39% of those not adherent to medication\textsuperscript{10} (Figure 2). In another study of a European version of Pentasa®, 362 ulcerative colitis patients in remission were given 2g once-daily or 1g twice-daily for 12 months\textsuperscript{11}. The difference in remission rates by the end of the study (71% with once-daily and 59% with twice-daily, P=0.024) was completely confounded by adherence to therapy. All differences disappeared when adherence to therapy was included in the analysis.

Conclusions

Once remission is induced, 5-ASA maintenance is critical, for both maintenance of remission and for colorectal cancer chemoprevention. Since adherence to maintenance therapy is very low, it is incumbent on physicians to:

- Use a once-daily 5-ASA formulation to simplify dosing regimens
- Educate patients about the large benefits of maintenance therapy
- Choose the best agent for the patient based on adherence issues, such as cost, number of tablets, and dosing regimens.

References:


