# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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## The Role of Aminosalicylates in Crohn's Disease

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### G&H Could you describe the initial studies of the 5-aminosalicylates for Crohn's disease?

**TB** The first product containing 5-aminosalicylate (5-ASA) was sulfasalazine. This agent was found to be effective in ulcerative colitis (UC), and it was thought that the reason for its effectiveness was because bacteria split the sulfapyridine and 5-ASA molecule. 5-ASA is absorbed in the duodenum and is then excreted in the bile, at which point it enters the colon, where it is split by bacteria.

Studies were conducted to further evaluate the efficacy of 5-ASA. In one study, patients with UC were given one of three different enemas, one containing sulfasalazine, another containing the antibiotic sulfapyridine, and a third containing 5-ASA.[1] Patients who received the 5-ASA enema had a much better response than those who received sulfapyridine. The same study was then repeated with suppositories and included a few patients with Crohn's disease involving the rectum. Again, 5-ASA was confirmed as the active moiety of sulfasalazine.[2] This finding was taken to be evidence that 5-ASA was the active ingredient, and led to the development of topical 5-ASAs, suppositories, enemas, and other ways to deliver 5-ASA.

### G&H Has the mechanism action, in which bacteria split the molecule, been confirmed over the years of 5-ASA use?

**TB** One of the observations that has been made outside of the clinical trial setting is that patients with ileitis appear to benefit from sulfasalazine therapy, raising the question of whether the entire molecule might be effective, rather than only the split products. In the study by Azad Khan et al,[1] both the sulfasalazine enema and the 5-ASA enema were effective. It is safe to assume that there was no stool in the rectum or, if there was stool present, there would not have been time for bacteria to split the 5-ASA. Therefore, it seems logical to hypothesize that sulfasalazine as a molecule is also effective.

In addition, patients with esophageal Crohn's disease (CD) or gastric or upper gastrointestinal CD have responded to sulfasalazine as an oral suspension, supporting the hypothesis that the whole molecule is effective, not only the split product. Interestingly, a case study was reported several years ago in which a piece of colon was used to create an artificial vagina. The patient developed UC in which bleeding that occurred in the transplanted colon tissue was treated effectively with sulfasalazine; the bleeding stopped in all areas. This case indicates that sulfasalazine was absorbed and worked through the bloodstream to stem the vaginal bleeding; this benefit could not have been due to contact with bacteria because the sulfasalazine was not in the vagina.

These findings point to the possibility of the entire molecule being effective, and of the possible efficacy of 5-ASA in the small bowel. However, no controlled trial has been conducted, and there is not much in the literature on the efficacy of sulfasalazine in the small bowel.

### G&H Are 5-ASAs best used in combination or as single agents in the treatment of CD?

**TB** While clinical trials of 5-ASA for CD have mainly been single-agent studies, it has been observed over the years that the 5-ASA agents are most likely more effective in combination with other agents, such as steroids. The National Cooperative Crohn's Disease Study did not confirm a benefit for adding sulfasalazine to prednisone,[3] but anecdotal experience has shown that adding a 5-ASA to another agent in a patient who is not doing well can be beneficial. However, 5-ASAs will not enable steroid-dependent patients to become steroid independent, and 5-ASAs will not replace azathioprine.

### G&H What have clinical trials found about the role of 5-ASAs in CD?

**TB** Often, the clinical studies have been at odds with clinical experience, not showing a benefit even though physicians have observed 5-ASAs to be effective. A meta-

analysis concluded that the best setting in which to use 5-ASA is postoperatively. A large dose of 5-ASA (3 g) was associated with decreased recurrences of CD, but with only 1 responder among 9 patients. The problem with this study is that it included patients with a variety of indications for surgery. Patients with active disease that would be expected to recur experienced the best response.

Prantera and colleagues[4] conducted a study in which 5-ASA was given at a dose of 2.4 g in patients with mild to moderate ileitis who had never undergone surgery, had no complications, and had not been treated with prednisone. In this patient population, 5-ASA showed a statistically significant benefit. The cumulative relapse rate at 12 months was 28% among patients receiving 5-ASA and 55% among patients receiving a placebo.

Another study, by Singleton and coworkers,[5] found that a reasonable response could be obtained in patients with ileitis using up to 4 g of mesalamine (Pentasa, Shire). This finding led many clinicians to use 16 mesalamine tablets for ileal colitis. Remission occurred among 43% of patients receiving mesalamine and 18% of patients receiving placebo. However, a meta-analysis of this and two subsequent trials demonstrated a statistical benefit, but only by less than a 20-point difference in the Crohn's Disease Activity Index.[6,7] Hence, the data for mesalamine for active or maintenance therapy is modest at best.

## G&H What is your approach to using the 5-ASAs?

**TB** Most often, I combine a 5-ASA with another agent, usually an antibiotic, because there is some evidence that luminal bacteria play a role in CD. If the patient does not respond to this approach, I continue 5-ASA use. Many clinicians proceed to use budesonide (Entocort, Prometheus), which has been approved for maintenance therapy and, in a short-term comparison trial, was superior to treatment with mesalamine in ileo-cecal Crohn's disease for up to 16 weeks[8]; the average remission time with budesonide is 7 months, versus 3 months seen with a placebo. However, I continue to use a 5-ASA, often a mesalamine formulation (Pentasa or high-dose Asacol [Procter & Gamble]), because it seems to work by a different mechanism than that of budesonide. This approach has not been proven to be effective in a clinical trial, but I always use combination therapy; I do not administer prednisone or budesonide alone.

In addition, if a patient is going to be treated with azathioprine or 6-mercaptopurine (6-MP), I will continue treatment with 5-ASA drugs because the 5-ASAs inhibit thiopurine S-methyltransferase, thereby prolonging the efficacy of azathioprine or 6-MP. However, if a patient being treated with azathioprine or 6-MP has a low or borderline white blood cell count, then I will not add 5-ASA to his or her treatment regimen. The addition of a 5-ASA would most likely increase the amount of circulating 6-thioguanine, the active ingredient of azathioprine, and further lower the white blood cell count.

If a patient has undergone surgery for inflammation, I might use 5-ASA, perhaps with an antibiotic, and will have the patient undergo a colonoscopy at 6 months in order to determine if the disease is actively recurring. If the disease is actively recurring, I would most likely add azathioprine to the treatment regimen.

The most common CD setting in which I use 5-ASAs is mild to moderate disease, and I would continue to use these drugs in patients who are also receiving budesonide, azathioprine, or 6-MP. Importantly, there are no good controlled trials supporting this approach; it is based on clinical experience that 5-ASAs are effective in this setting and work by a different mechanism than other agents used to treat CD. Many clinicians do not use 5-ASAs as maintenance therapy, but my recommendation is to continue them at the dose at which a remission was obtained.

## G&H Why is there a discrepancy between trial findings and physicians' experience?

**TB** Many studies showing that 5-ASA has not been proven to be useful in CD are older, and the trials done two or three decades ago were not done as well as current trials are. The National Cooperative Crohn's Disease Study, which was conducted in the late 1970s/early 1980s, was a null hypothesis study[3]; it was designed to show that no agent would change the course of CD. The benefit had to be quite dramatic in order to be confirmed statistically, and the 5-ASAs were not found to be effective. When discussing combination approaches, this study is not entirely relevant. It could be a mistake to focus solely on the findings of controlled trials when extensive clinical experience has found a certain approach to be useful.

## Suggested Reading


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