Searching for the Delta: 5-Aminosalicylic Acid Therapy for Crohn's Disease

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Abstract: Crohn's disease (CD) is a chronic inflammatory condition that often requires lifelong medical therapy for the induction and maintenance of remission. Oral mesalamine (5-aminosalicylic acid [5-ASA]) therapy has several forms, which can be categorized into oral formulations and prodrugs. The ability to demonstrate the efficacy of 5-ASA is limited in most clinical trials by the nonspecific endpoints of the Crohn's Disease Activity Index. Overall, clinical trials have not shown 5-ASA therapy to be superior to placebo for the induction of remission, with the exception of sulfasalazine in colonic CD. 5-ASA therapy has also not been shown to be superior to placebo for maintenance of medically induced remission; however, mesalamine may have a modest effect in surgically induced remission. Further research is needed regarding the optimal monitoring and therapy for patients with mild CD who often achieve remission with placebo in clinical trials.

Crohn's disease (CD) represents a spectrum of chronic inflammation and its sequelae, which may occur anywhere in the gastrointestinal tract from the mouth to the anus.[1] The incidence of CD is approximately 6–8 per 100,000 individuals, its prevalence is approximately 130–170 per 100,000 individuals, and approximately 500,000–1 million individuals are affected in the United States.[2,3] CD is diagnosed either by observation of symptoms combined with endoscopic and histologic criteria, or, with less specificity, by endoscopic and radiologic criteria.[4] Inflammation in CD is generally progressive in nature and proceeds to stricturing or penetrating disease in 60% of patients.[5] CD severity can be measured by symptoms, complications, laboratory parameters, radiologic changes, or endoscopic examination of the affected mucosa. Disease that is refractory to therapy or that involves strictures, fistulae, or abscesses may require surgical therapy. After approximately 1 year of disease, 35% of patients may undergo surgery.[6,7] Within 10 years after diagnosis, nearly 50% of CD patients may undergo surgery.[7] Given clinicians' lack of knowledge regarding the etiology of CD, current medical therapies are directed at reducing inflammation and

inducing and maintaining disease remission in order to improve patients' symptoms and decrease complications and sequelae.

Medical therapy options for inflammatory CD include mesalamine (5-aminosalicylate [5-ASA]) therapies, which are available both as oral delayed-release and sustained-release formulations and as prodrugs; immunomodulators (thiopurines and methotrexate); ileal release budesonide; and biologic therapies (infliximab [Remicade, Centocor], adalimumab [Humira, Abbott], certolizumab pegol [Cimzia, UCB], and natalizumab [Tysabri, Elan/Biogen Idec]; Table 1). Medical therapy outcomes and clinical trials of these medications are often categorized by their ability to achieve induction of response or remission during a period of active disease, to maintain medically induced remission, or to maintain surgically induced remission. 5-ASA does not have a role in the management of fibrotic strictures or fistulizing CD. This paper will focus on studies assessing the efficacy and safety of 5-ASA in inflammatory CD and implications of these studies for clinicians and patients.

Table 1. Medical Therapy Options for Inflammatory Crohn's Disease

- **Mesalamine (5-aminosalicylate) therapies**
  - Oral delayed-release and sustained-release formulations
  - Prodrugs
    - Sulfasalazine
    - Olsalazine
    - Balsalazide
- **Immunomodulators**
  - Thiopurines
  - Methotrexate
- **Ileal release budesonide**
- **Biologic therapies**
  - Infliximab
  - Adalimumab
  - Certolizumab pegol
  - Natalizumab

Pharmacology

The differences in 5-ASA compounds are important to consider when assessing their efficacy in CD. Approximately 30% of patients with CD have only large bowel involvement; therefore, an examination of 5-ASA therapy should be stratified by medicine type (prodrugs vs oral delayed-release or sustained-release formulations) when evaluating the agent's effect on small bowel versus colonic CD, since prodrugs are unlikely to have an effect on small bowel CD.[8]

The colonic-release prodrug preparations that have been studied in randomized controlled trials (RCTs) of CD include sulfasalazine and olsalazine (Dipentum, Pfizer). When sulfasalazine reaches the colon, its azo bond is broken by azo reductase produced by colonic bacteria, which leads to the production of 5-ASA and sulphapyridine.[9] 5-ASA remains in the colon, while sulphapyridine is absorbed. Studies have shown that sulphapyridine functions only as a carrier molecule.[10] The relative molecular weights that can be used to compare effective doses of 5-ASA between prodrugs and mesalamine are as follows: sulfasalazine 398.40, olsalazine 345.21, and mesalamine 153.14.[11]

The coatings of oral delayed-release and sustained-release 5-ASA preparations are associated with different release characteristics within the intestine. When administered orally, free 5-ASA is quickly absorbed and metabolized in the proximal small intestine.[11] The oral delayed-release preparations are formulated with different Eudragit coatings. Eudragit-S coating, which is used for delayed-release mesalamine (Asacol, Warner Chilcott), releases at or above a pH of 7 and delivers medicine to the terminal ileum. Eudragit-L coating—which is used for Salofalk (Dr. Falk Pharma), Claversal (Merckle), and Mesasal (GlaxoSmithKline)—releases at or above a pH of 6 and delivers medicine to the distal ileum.[11] Controlled-release mesalamine capsules (Pentasa, Shire), formulated with ethylcellulose-coated microgranules, release in the duodenum, jejunum, ileum, and colon.

A proportion of the 5-ASA released by both prodrugs and oral mesalamine formulations is absorbed and metabolized by the small bowel and/or colon, while the rest of the 5-ASA is excreted into the stool.[12] Sandborn and Hanauer examined the pharmacokinetic profiles of oral 5-ASA formulations in chronic ulcerative colitis.[11] Their systematic review showed that the systematic absorption and fecal excretion of oral mesalamine and prodrugs are comparable. An exception was that the Eudragit-L form is more quickly absorbed in the small bowel. This analysis refuted the concept that prodrugs decrease systemic absorption of 5-ASA or that they leave more active 5-ASA for release in the distal colon.[11] These results imply that there may be little difference between oral mesalamine and prodrugs in terms of their effect on colonic CD, and the choice of drug can depend instead on dosing, cost, or differences in proximal release for patients with ileocolonic disease.

Measurements of Crohn's Disease Severity and Efficacy

In clinical trials assessing the efficacy of 5-ASA in CD, disease activity (ie, remission vs mild, moderate, or

severe disease) at enrollment and in response to therapy is most often measured by the Crohn's Disease Activity Index (CDAI). The CDAI was developed by Best and Singleton in 1970–1971 for the National Cooperative Crohn's Disease Study (NCCDS) and was originally based on 112 patient visits at 13 medical centers.[13,14] The CDAI variables for disease activity are those most closely associated with physicians' rating of disease status. Physicians' ratings of overall well-being and abdominal pain are weighted heavily; the index also includes data on the number of soft stools per day, extraintestinal complications (including fissures, fistulae, and abscesses), use of antidiarrheal medication, abdominal mass on examination, hematocrit, and weight change.[14] The index lacks specificity for CD as the cause of these symptoms. Disease severity cutoffs were set at less than 150 points for quiescent disease or remission, 150–450 points for mild-to-moderate disease, and greater than 450 points for severe disease.[14]

The efficacy of 5-ASA compared to placebo for induction of remission or response has primarily been assessed in patients with mildly to moderately active CD.[15] Trials have reported variable average decreases in CDAI scores with therapy, but close analysis has determined that a decrease of 50 points is the minimum difference a clinician can detect.[16] Confounding concurrent illnesses may include irritable bowel syndrome, small bowel bacterial overgrowth, functional chronic abdominal pain, and bile salt diarrhea. In addition, a patient's CDAI score can be affected by extraintestinal manifestations or fistulae, which do not respond to 5-ASA therapy and may not mirror bowel disease activity. The CDAI score has been modified with the prospectively validated Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simplified Endoscopic Score for Crohn's Disease (SES-CD); these scores correlate strongly with each other but correlate weakly with CDAI score or C-reactive protein (CRP) level.[17-19] Ultimately, the use of the CDAI as a clinical trial's primary endpoint limits its ability to assess the effect of 5-ASA on bowel inflammation in CD. Future trials using the CDEIS or SES-CD as primary endpoints may help identify which treatments reduce inflammation in CD; because the CDAI is routinely used, however, a current benefit of its use is that it allows researchers to pool and compare trials of 5-ASA in CD.

Induction of Remission

When assessing 5-ASA's efficacy in the induction of mildly to moderately active CD, a stratified examination of both prodrugs and oral preparations is helpful because prodrugs generally do not have any clinical effect in the small bowel.

A large proportion of the prospective RCT evidence regarding the efficacy of 5-ASA in the induction of remission (defined as a CDAI <150 points) comes from 2 early studies of sulfasalazine in the treatment of active CD. Part 1 of the NCCDS examined 295 patients with active CD who were randomized to 1 g/15 kg sulfasalazine (4–6 g/day), azathioprine, or placebo for 17 weeks.[13] Overall, 43% (32/74) of patients treated with sulfasalazine versus 30% (23/77) of patients in the placebo group achieved remission (P=.088); however, patients with colitis were more likely to respond to the prodrug than placebo (P=.027).[13]

A second study, the European Cooperative Crohn's Disease Study (ECCDS), randomized 455 patients to sulfasalazine (3 g/day), 6-methylprednisolone, or placebo.[20] Only 1 method of outcome analysis, "failure and relapse" (defined as CDAI >150 points after the first 6-week period), showed a beneficial effect for sulfasalazine over placebo; notably, this benefit occurred in patients with active and previously treated colonic disease.[20] There was no significant difference in the proportion of patients achieving remission at 16 weeks (sulfasalazine, 27/54 [50%]; placebo, 22/58 [38%]; P=.20).[20]

Lim and Hanauer recently published a pooled analysis of 2 trials that showed a modest relative risk (RR) for inducing remission with sulfasalazine of 1.38 (95% confidence interval [CI], 1.02–1.87; P=.04; number needed to treat [NNT]=8).[15] Corticosteroids were significantly more effective at achieving remission in active disease in 2 trials (pooled RR of sulfasalazine for remission=0.66; 95% CI, 0.53–0.81; P=.0001).[15]

Another prodrug, olsalazine, was examined by Wright and colleagues in a 1995 study involving 91 patients with active CD.[21] The intent-to-treat analysis, which was limited by a high rate of withdrawals due to diarrhea in the olsalazine group, showed placebo to be more effective than olsalazine for achieving remission (49% vs 17%, respectively; P=.001).[21]

The efficacy of different oral 5-ASA agents has also been evaluated in several RCTs that used the CDAI as a measure of remission. Rasmussen and coworkers randomized 67 patients to controlled-release mesalamine (1.5 g/day) or placebo and found no significant difference in the proportion of patients who were in remission at 16 weeks.[22] In 1993, Singleton and colleagues compared controlled-release mesalamine at various doses (1 g/day, 2 g/day, or 4 g/day) with placebo and also found no significant difference in remission at 16 weeks.[23] One year later, a subsequent study by the same group randomized 232 patients to controlled-release mesalamine (2 g/day or 4 g/day) or placebo; the only significant difference in this study was between placebo and the controlled-release mesalamine 4 g/day dosage (43% vs 18%; P=.001).[24] A

subsequent, larger, unpublished RCT—the Crohn's III trial—assigned 310 patients to either controlled-release mesalamine 4 g/day or placebo. No significant difference was found in terms of change in CDAI scores (–72 vs –64; weighted mean difference –8; 95% CI, –33 to –17).[15]

Tremaine and colleagues at Mayo Clinic randomized 38 patients to delayed-release mesalamine 3.2 g/day or placebo. No significant difference in the percentage of patients achieving remission was found; however, there was a trend toward better performance with delayed-release mesalamine versus placebo (45% vs 22%) despite this study's limited statistical power.[25] A systematic review and pooled analysis performed by Lim and Hanauer in 2010 evaluated delayed-release mesalamine compared to placebo for achieving remission and found no significant difference.[15]

Two RCTs have examined the efficacy of 5-ASA compared to budesonide for achieving remission. In 1998, Thomsen and colleagues randomized 182 patients to controlled-release mesalamine (4.8 g/day) or budesonide for 16 weeks. The proportions of patients achieving remission in the controlled-release mesalamine and budesonide groups were 34% and 60%, respectively (P=.001).[26] A recent noninferiority study by Tromm and the International Budenofalk Study Group examined 390 patients who received budesonide (9 mg/day) or the Eudragit-L–coated mesalamine formulation Salofalk.[27] Study participants had mild-to-moderate disease activity as defined by the CDAI; however, 55–60% of patients had an erythrocyte sedimentation rate (ESR) less than 20 mm/hr or a CRP level less than 10 mg/L. The proportions of patients achieving remission at 8 weeks were relatively large in both groups (70% and 62% for the budesonide and Salofalk groups, respectively; P=.001 for a predefined noninferiority margin of 10%).[27] In a subgroup analysis, budesonide was superior to Salofalk among patients with an ESR greater than 20 mm/hr.[27] The impact of this study's use of pH-dependent release (Budenofalk) versus controlled-release budesonide (Entocort, AstraZeneca) formulations is unclear. Overall, this study found a small, nonsignificant, symptomatic benefit for budesonide over Salofalk in a group of patients with heterogeneous disease location and probably mild inflammation.

Maintenance of Remission

CD is a chronic inflammatory condition that is currently a lifelong disease. Presently, we are unable to accurately and reliably predict which individuals will progress to sequelae of CD such as strictures, fistulae, and abscesses. Therefore, a maintenance medication is indicated for nearly all patients with CD in order to decrease the likelihood of relapse and potentially change the progressive natural history of CD. To specifically examine the efficacy of 5-ASA as maintenance therapy, analyses should ideally include only patients who are in remission at the onset of the study and then determine the proportion of patients who experience relapse, which is often defined as a CDAI score greater than 150 points.

The 1979 NCCDS demonstrated no significant difference between sulfasalazine and placebo for maintenance of remission, despite this study showing modest efficacy for sulfasalazine in the induction of remission in colonic CD.[13] In the 1984 ECCDS, sulfasalazine was no more effective than placebo for the maintenance of remission among patients with inactive disease upon entry into the study.[20] A subsequent, relatively large, prodrug study conducted in 2001 by Mahmud and colleagues randomized 327 patients in remission without proximal small bowel CD to either olsalazine or placebo.[28] At 12 months, there was no significant difference in relapse rates (CDAI >150 points) between the 2 groups among patients with ileocolitis or colitis; however, the percentage of patients who withdrew from the study was higher in the olsalazine group than the placebo group (65.4% vs 53.9%; P=.038).[28]

A larger study of oral delayed-release 5-ASA for maintenance of remission is a 1990 study by the International Mesalazine Study Group that evaluated Mesasal/Claversal (1.5 g/day) versus placebo.[29] No significant difference in relapse rates was found at 12 months (49/125 [39%] vs 52/123 [42%], respectively).[29] Similarly, Thomson and colleagues found no significant difference in relapse rates among 207 patients randomized to Mesasal/Claversal (3 g/day) or placebo over 12 months.[30] Likewise, Sutherland and colleagues randomized 293 CD patients who were in remission to maintenance therapy consisting of either controlled-release mesalamine (3 g/day) or placebo. At 48 weeks, there was no significant difference in relapse rates between 5-ASA therapy (25%) and placebo (36%).[31] In contrast to these studies, a 24-month study by Gendre and colleagues randomized 161 patients to controlled-release mesalamine (2 g/day) or placebo and found a significant difference in relapse rates (defined as CDAI >250 points or CDAI of 150–250 points and >50 points over baseline) among the strata of patients who had been in remission less than 3 months (29% vs 45%, respectively; P<.003).[32]

A systematic Cochrane review conducted by Akobeng and Gardener in 2005 examined 7 RCTs that compared 5-ASA to placebo for the maintenance of medically induced remission in patients with inactive CD.[33] Six studies utilized CDAI scores, and 1 study utilized the Harvey-Bradshaw Index, an alternative index composed solely of clinical parameters (general well-being, abdominal pain, number of liquid stools per day, abdominal mass,

and complications).[34,35] The fixed-effects odds ratio (OR) was 1.00 (95% CI, 0.8–1.24) for the six 12-month studies that compared 5-ASA to placebo and 0.98 (95% CI, 0.51–1.90) for the 24-month study by Gendre and colleagues.[32,33] Overall, there is no evidence that 5-ASA is better than placebo for maintaining medically induced remission as defined by the CDAI.

The role of 5-ASA in maintaining surgically induced remission has been examined in 2 recent systematic reviews.[36,37] Rutgeerts and colleagues demonstrated that most patients (75%) relapse endoscopically within 1 year of surgery, and some patients (20%) will relapse symptomatically.[38] Ford and colleagues identified 11 RCTs examining 5-ASA versus placebo for maintenance of postsurgical remission.[36] These studies utilized sulfasalazine or mesalamine at varying doses and used various definitions of relapse (ie, CDAI >150 points, CDAI >250 points, clinical evidence of relapse, endoscopic recurrence, or radiologic relapse). A pooled estimate of efficacy for maintenance of remission over periods ranging from 33 weeks to 3 years showed a modest improvement for 5-ASA over placebo (risk ratio, 0.86 [95% CI, 0.74–0.99]; NNT=13 [95% CI, 7–50]).[36] In addition to the overall analysis, the meta-analysis was stratified by medication class and included 5 studies of sulfasalazine and 6 studies of mesalamine. The studies of sulfasalazine showed no significant difference between treatment and placebo (risk ratio, 0.97; 95% CI, 0.72–1.31), while the studies of mesalamine versus placebo showed a modest statistical benefit for 5-ASA in maintaining postsurgical remission (risk ratio, 0.86; 95% CI, 0.74–0.99).[36]

Gordon and colleagues identified 9 RCTs of at least 6 months' duration in which 5-ASA was compared to either placebo or azathioprine.[37] Treatments varied from sulfasalazine (3 g/day) to controlled-release mesalamine (3 g/day or 4 g/day), and definitions of relapse included a CDAI score greater than 150 points; a CDAI score greater than 250 points; or clinical, radiographic, or endoscopic relapse. In the pooled analysis, 5-ASA was again modestly superior to placebo for preventing relapse (OR, 0.68; 95% CI, 0.52–0.9; NNT=16–19).[37] A study by Caprilli and colleagues, which compared delayed-release mesalamine (2.4 g/day) to placebo over 12 months, is noteworthy due to its efficacy estimate and endpoint. Although this study was an open-label RCT, endoscopic evidence of relapse occurred in 22 of 55 patients (40%) compared to 36 of 55 controls (65%) at 1 year.[39] In a pooled analysis of 2 studies, there was no significant difference in thiopurine versus 5-ASA for preventing relapse (OR, 1.08; 95% CI, 0.63–1.85).[36,40,41] Of note, the thiopurine dose used in the study by Hanauer and colleagues was relatively low (6-mercaptopurine at 50 mg/day).[41] A recent study by Reinisch and colleagues examined differences in clinical relapse (defined as CDAI ≥200 points and an increase >60 points) between azathioprine (2–2.5 mg/kg/day) and Salofalk (4 g/day) in patients with endoscopic recurrence.[42] At 1 year, there was no significant difference in treatment failure between patients treated with azathioprine and those who received 5-ASA; however, clinical recurrence was less frequent with azathioprine than with 5-ASA (0% vs 11%; P=.031), and drug discontinuation was greater in the azathioprine group than in the 5-ASA group (22% vs 0%; P=.002).[42]

Overall, the heterogeneity in study medications and outcomes makes it difficult to draw a clinical inference from pooled results. However, there appears to be a modest benefit for 5-ASA in the postoperative setting. It remains unclear why this modest signal for efficacy of 5-ASA over placebo is seen among CD patients in potentially the "deepest" remission, and it is notable that endpoints other than the CDAI (ie, endoscopic and radiologic findings) comprise a larger proportion of these data than the pooled efficacy data from RCTs of medically induced remission.

Safety and Costs

In 2 studies reporting adverse events associated with the use of 5-ASA for the induction of remission, there was no significant overall difference in adverse events between 5-ASA and placebo.[23,25] Rates of adverse events in studies of 5-ASA compared to placebo for maintenance of medically induced remission are similarly low.[33] A pooled analysis of the safety of 5-ASA versus placebo in the maintenance of postsurgical remission also showed no significant difference in 4 trials.[37]

Although high levels of 5-ASA have been associated with interstitial nephritis in animal models, standard doses of 5-ASA and its metabolites yield human plasma concentrations that are substantially lower than plasma levels for recommended doses of aspirin.[11,43] Sandborn and Hanauer followed 2,940 patients who were taking 5-ASA (up to 7.2 g/day) for up to 5 years and found no significant adverse effects related to duration or dose.[11] Interstitial nephritis reported in patients taking 5-ASA may instead be dose-independent hypersensitivity or related to disease activity.[11] Nonetheless, in order to detect the rare patient who develops a potentially end-stage kidney disease while taking 5-ASA, it is prudent to monitor creatinine levels and potentially perform urinalysis shortly after the onset of 5-ASA therapy and approximately yearly thereafter.

For obvious reasons, there are no RCT data on the safety of 5-ASA versus placebo in CD during pregnancy. However, both retrospective and prospective population-based studies have been conducted, and these studies

demonstrate no increased risk for congenital abnormalities, stillbirth, spontaneous abortion, or low birth weight.[44-47] 5-ASA products are classified as pregnancy category B drugs, with the exception of regular-dose and high-dose delayed-release mesalamine, which have a Eudragit-S coating that contains dibutyl phthalate, a chemical associated with urogenital defects in male offspring of pregnant rodents receiving more than 190 times the human dose.[48] Because sulfasalazine inhibits transportation of folate, folic acid (1 mg daily) should be administered with the medication.[49] Sulfasalazine also reduces sperm motility and should be discontinued 3 months prior to planning conception.[50] The small risks of these medications in pregnancy are balanced against their potential benefit in helping a mother maintain remission of her disease. However, it is important to keep in mind that the evidence base as presented here and elsewhere shows no benefit for maintaining medically induced remission and only modest effect in the postoperative setting.

The costs of 5-ASA in CD are potentially substantial. Kappelman and colleagues estimated the direct costs of CD in the United States from an insurance claims database in 2003–2004 and found that oral 5-ASA was estimated to cost $495 per patient-year (standard deviation, $768), and 39% of patients had at least 2 claims during the year.[51]

Summary

CD is a lifelong, relapsing, inflammatory condition for which patients seek medical therapy in order to improve symptoms and decrease the risk of progression, complications, and surgery. Studies have shown that 5-ASA therapy is only modestly superior to placebo for inducing symptomatic remission in the subgroup of patients with colonic disease who are taking sulfasalazine. 5-ASA therapy has not been shown to be more effective than placebo for maintaining medically induced remission. There may be a role for postoperative 5-ASA in patients without risk factors for recurrent surgery (such as mucosal ulceration, smoking, or predictors of disabling course).[38,52,53]

The inability to travel down this river of clinical evidence and find a beneficial "delta," or incremental improvement, for 5-ASA over placebo is confounded by the nonspecific nature of the CDAI inclusion criteria and outcomes in RCTs. Nonetheless, synthesis of the available clinical studies does not provide an evidence-based rationale for induction or maintenance treatment with 5-ASA in most patients. Future RCTs that include endoscopic or radiologic primary endpoints may be better able to measure the anti-inflammatory effect of 5-ASA in CD. Although placebo effect rates have been generally high in these studies, 5-ASA therapy is associated with significant costs and rare but real risks; a pill is not necessary to obtain placebo response rates.[54] The best evidence-based therapy for mild, small bowel CD or CD without predictors of early postoperative recurrence may be an ongoing therapeutic relationship between the clinician and the patient that consists of symptom management, disease monitoring, and preventative counseling.

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