Clinical Medicine Insights: Gastroenterology

REVIEW

Medical Management of Ulcerative Colitis with a Specific Focus on 5-Aminosalicylates

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Abstract: Medical management of ulcerative colitis has continued to evolve over more than half of a century. Perhaps, the important advance was the development of sulfasalazine, a drug initially used for the treatment of inflammatory joint disease and only later in the treatment of inflammatory bowel disease. Sulfasalazine was a combination designer drug consisting of sulfapyridine, a sulfa-containing antibacterial agent, and 5-amino-salicylate (5-ASA), an anti-inflammatory agent. Its value appeared to be its ability to target a therapeutic concentration of the 5-ASA component of the medication primarily in the colon, largely avoiding proximal small intestinal absorption. With increasing experience, however, it also became evident that many patients treated with sulfasalazine developed intolerance to the drug and, in some rare instances, serious drug-induced hypersensitivity reactions, largely to the sulfapyridine portion. As a result, a number of alternative forms of delivery of 5-ASA were developed consisting of either a similar sulfasalazine-like prodrug formulation requiring luminal destruction of an azo-bond releasing the 5-ASA or a pH-dependent 5-ASA packaging system that permitted release in the distal intestine, particularly in the colon. As a result, 5-ASA—containing medications continue to provide a valuable management tool for remission induction in mildly to moderately active distal or extensive ulcerative colitis, an additional option for more severely symptomatic disease and value for maintenance therapy with limited potential side effects, even with long-term use.

Keywords: inflammatory bowel disease, ulcerative colitis, biological agents, sulphasalazine, mesalamine, corticosteroids, immuno-suppressants, cyclosporine

Clinical Medicine Insights: Gastroenterology 2012:5 77–83

doi: 10.4137/CGast.S8673

This article is available from http://www.la-press.com.

Introduction

Treatment of idiopathic ulcerative colitis remains highly personalized despite various published algorithms and excellent practice guidelines that have been detailed for different countries in the Americas, Europe, and Asia.[1–3] This review will focus on a practical and individualized approach to management, particularly as treatment relates to 5-aminosalicylate—containing medications rather than other agents, such as steroids and immunosuppressants (ie, azathioprine), biologicals (eg, infliximab), or calineurin inhibitors. In general, medical treatment of ulcerative colitis follows an accurate diagnosis (especially exclusion of an expanding array of infectious agents that may create a similar initial clinical illness or be superimposed on ulcerative colitis, particularly cytomegalovirus and *Clostridium difficile* infections), an overall clinical evaluation of the patient, that includes consideration of other concomitant medical problems, documentation of drug tolerance and hypersensitivities and, finally, assessment of a host of other issues that may influence the treatment decision-making process. These issues include availability of care, especially for patients living in isolated or rural areas compared with urban centers with tertiary and quaternary levels of expertise. Other issues include concomitant availability of imaging and surgical expertise, patient's occupation and family support situation and, importantly, the costs implicit in different treatment options available in the proposed medical care plan. In some countries, funding for medical care is provided through either government or private sources (or both); therefore, funding source may be a significant consideration.

In addition, regulatory agencies in different countries may have approved a medication, but only for specific indications or may not have provided formal approval. Finally, in this era of social media, information on different medical therapies has become readily available, and specialist physicians have an important role in the accurate interpretation of available data on treatment options and their potential adverse effects.

Goals of Therapy

The current overall goal of medical management of ulcerative colitis is to induce clinical remission and, as a result, quality of life. Medical management of ulcerative colitis depends on an initial assessment of the clinical severity of the disease, confirmation of the diagnosis, which usually involves endoscopic and histologic examinations, and evaluation of the extent of the disease. Imaging of the disease is best done early in the course of the evaluation and prior to initiation of treatment, if possible, and subsequently if a change in management is contemplated. Because of the rapid evolution of modern endoscopic technologies, especially with high-definition colonoscopes and digital imaging, high quality photo documentation is now feasible throughout the colon. This has permitted development of serial imaging files on the macroscopic appearance of the disease in individual patients for comparative purposes over time. This is crucial for clinicians in evaluation of individual patients as well as in the performance of clinical trials because of the reported observer variation in describing macroscopic mucosal appearances for proctocolitis by experienced clinicians caring for patients suffering from inflammatory bowel disease.[4] In addition, the correlation between patient clinical status and endoscopic (as well as histopathological) changes in the colonic mucosa has shown some limitations.[5] Assessment of mucosal healing in inflammatory bowel disease has been reviewed elsewhere,[6] and this remains a critical issue in management. Simplified endoscopic scoring methods have been developed in ulcerative colitis,[7,8] and a detailed and excellent review of endoscopic endpoints used in inflammatory bowel disease, particularly ulcerative colitis, may be found elsewhere.[9] Longer-term studies have shown that evaluation of the effects of a treatment regimen on the endoscopic appearance, in addition to the clinical response to treatment, may be important. In particular, evidence suggests that if mucosal "healing" can be achieved, the prognosis may be optimized.[10] New clinical trials in ulcerative colitis now generally include mucosal healing because of a possible influence on long-term remission, complications (particularly colon cancer), need for colectomy, and quality of life.[11] Finally, the age of the patient at diagnosis is important. Recent studies have implied that younger patients, particularly in the pediatric age group, often have more severe disease.

Classification of Patients Depending on Extent of Disease

Because of improved diagnostic modalities, particularly endoscopic imaging, patients with idiopathic ulcerative colitis may now be classified—depending on the extent of mucosal involvement—as localized disease or proctitis, distal or left-sided disease, and more extensive colitis that usually extends in a continuous pattern proximal to the splenic flexure. In some patients with extensive disease, pan-colonic involvement occurs. The degree or severity of clinical features often appear to mirror the extent of disease involvement, although some patients with involvement localized to the rectum alone may present only with constipation rather than diarrhea. Acute severe disease may also occur, often with the initial clinical episode, and may be referred to as severe or toxic colitis (as opposed to toxic megacolon, a disorder that generally requires colectomy rather than medical treatment). Finally, some patients with colitis have been described in recent years as "treatment-refractory," which refers largely to patients with idiopathic ulcerative colitis that fails to respond to traditional management, including corticosteroids and thiopurines. Some patients with idiopathic ulcerative colitis, however, may be potential candidates for a biological agent prior to pursuing colectomy.

Assessing the extent of involvement may also aid in management, particularly for an individual patient. For example, limited disease in the rectum may only require local therapy with topical 5-aminosalicylate—containing enemas or suppositories rather than orally administered forms of the medication. Of course, from a practical perspective, even with this option for treatment of localized rectal disease, some patients may still prefer oral treatment over rectal administration.

Classification of Patients Based on Clinical Severity

In addition to the extent of the disease, usually defined by endoscopic imaging along with histologic evaluation, clinical severity is often evaluated on the basis of the severity of symptoms. For ulcerative colitis, clinical severity has been traditionally defined as mild, that is, less than or equal to 4 motions daily or moderate, that is, more than 4 motions daily, with no signs of systemic toxicity (ie, pulse more than 90 per minute, temperature less than 37.5 °C, hemoglobin greater than 10.5 g/dL, or erythrocyte sedimentation rate less than 30 mm per hour).[12] Severe colitis has been defined by Truelove and Witts Criteria as more than 6 bloody motions per day with 1 or more of the signs of systemic toxicity.[13] C-reactive protein (CRP) has also frequently been used as an "objective" marker of the severity of the inflammatory process.[14]

Assessing the severity of the inflammatory disease process may enable further individualization of treatment. Mild to moderate disease may be treated initially with a 5-aminosalicylate—containing medication alone, whereas moderately severe disease may lead earlier to other treatment measures, such as a corticosteroid with or without an immunosuppressant (eg, azathioprine) to control the inflammatory disease process.

Treatment Options and 5-Aminosalicylates (5-ASA)

For the purposes of this discussion, the intended focus here relates to use of 5-aminosalicylates (5-ASA) rather than other or additional pharmacological or biological therapies that also have a potentially important role in medical management of some patients, particularly those with more severe disease activity. Of course, surgical treatment may also become a necessary option to be considered. In general, this 5-ASA class of agents forms the background of pharmacological management for ulcerative colitis patients, particularly those with mildly or moderately active disease. If these agents fail to provide sufficient disease control, then other agents may be provided in an additive manner. Some of these have a significant potential for important side effects. Such agents include corticosteroids, immune modifiers, and biological agents. Other agents, however, such as probiotics, may have limited impact.

Evidence indicates that the 5-ASA drugs have an important role in the pharmacological treatment of localized proctitis, left-sided colitis (or proctosigmoiditis), and more extensive colitis, either alone or in combination with other agents, for active treatment and maintenance of remission. If medical treatment fails or if a complication of the colitis develops, then total proctocolectomy with

ileal pouch-anal anastomosis is the recommended treatment in most patients, particularly those that require elective surgery.[15]

Sulfasalazine

Sulfasalazine is now largely, although not entirely, a historical pharmacologic agent that was composed of a sulpha portion and a 5-ASA portion. Many patients that have used and tolerated this medication for years see no reason to change to the newer forms of 5-ASA delivery that may be more costly, so they continue use. Sulfasalazine was initially used based on the hypothesis that the drug provided two critical elements in the treatment of ulcerative colitis. First, the sulfa moiety (or sulfapyridine) was thought to provide an antimicrobial effect because of the known antibacterial effects of other sulfa-containing medications. Second, the 5-ASA moiety was thought to be the key active component in the medication to produce an anti-inflammatory effect. Sulfasalazine had also been used in the treatment of the inflammatory joint disorder rheumatoid arthritis long before it became commonly applied in patients with ulcerative colitis.

In retrospect, sulfasalazine is now recognized to have acted largely as a prodrug delivery system. A small amount, perhaps 10%, appears to be absorbed in the small bowel, while the other 90% has been shown to reach the colon. This prodrug was shown to permit release of the 5-ASA moiety in the colonic lumen with destruction of an azo bond by azoreductases from luminal microflora. The sulfa-containing portion or sulfapyridine if administered alone is normally rapidly absorbed from the upper gastrointestinal tract with virtually no fecal elimination. Sulfapyridine, however, could also be systemically absorbed from the colon, transported to the liver, and acetylated. Acetylation was reported to be genetically programmed, with slow acetylators having higher levels of free sulfasalazine and more drug-induced adverse events.[16] The 5-ASA moiety, once released into the colonic lumen, was believed to be only partially absorbed with over 80% remaining within the colonic lumen (even though rapid absorption of 5-ASA can occur in the upper gastrointestinal tract if administered without a carrier component). Some of this component was acetylated by colonic mucosal cells and released in an acetylated form into the colonic lumen. Some luminal bacterial acetylation also was shown to occur. A small amount of 5-ASA is absorbed, while the 5-ASA component was believed to produce the anti-inflammatory effects in the colon (although this 5-ASA portion of the drug may also be absorbed from the lumen and/or metabolized to other derivatives). This sulfasalazine medication was largely used for induction of remission in mildly or moderately active ulcerative colitis with increasing doses from 2 to 4 grams daily producing an increasing clinical response. At higher doses, there appeared to be little added therapeutic benefit gained, although side effects increased dramatically at higher daily dose levels. Sulfasalazine was shown to be effective at doses of 2 to 6 grams per day, resulting in clinical remission in up to 80% of patients. Indeed, a dose-response curve from 1 to 4 grams per day appeared to be evident, with little improvement at higher doses of 6 grams per day or more.[17–19] In at least 20% of patients, however, side effects develop when the dose ranges from 1 to 4 grams per day and then appear to exponentially increase at doses of more than 4 grams per day.

Most of these side effects were limited and mild, although skin hypersensitivity reactions were common and often troublesome. Rarely, other more serious side effects were noted (eg, bone marrow effects and liver disease). Potential significant side effects of the sulfapyridine component have been detailed elsewhere[20] but are also tabulated in Table 1. Another potentially important side effect of sulfasalazine was the recognition of its potential to alter sperm and result in male infertility. Cessation of the medication suggested that this medication-related effect was reversible. Finally, in patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a predisposition to development of drug-induced hemolysis was noted along with the potential for folatedeficiency—induced anemia due to inhibition of folic acid absorption by sulfasalazine.

In some patients experiencing tolerance difficulties, side effects were largely treated in a supportive manner coupled with drug cessation. For other patients, however, complex programs of desensitization were empirically developed with gradually increased dosage amounts of sulfasalazine administered over

Table 1. Sulfapyridine tabulated side effects.[20,22–26]

Endocrine
Goiter and/or thyroid function disturbance
Gastrointestinal
Diarrhea
Anorexia, nausea and vomiting
Hematologic
Leukopenia and/or thrombocytopenia
Agranulocytosis
Aplastic anemia
Hypersensitivity
Skin rash, pruritis, urticaria
Fever and photosensitivity
Erythema nodosum
Stevens-Johnson syndrome
Lyell's or Behcet's syndrome
Toxic epidermal necrolysis
Serum sickness syndrome
Hepatitis
Renal
Crystalluria and hematuria
Reduced creatinine clearance

many weeks.[21] Since most intolerance to sulfasalazine was believed to be due to the sulfa portion of the drug, alternative modes of delivery of the 5-ASA component were also developed to circumvent the side effects of the sulfapyridine moiety.

Newer 5-ASA Medications

Some of the newer 5-ASA preparations include olsalazine (Dipentum), balsalazide (Colazide), and mesalamine, each having different kinetics for drug delivery and site of action and lacking the sulfa-containing component. Although these "modern" 5-ASA preparations did not appear to exceed the clinical effectiveness of sulfasalazine, their clinical effects appeared to be comparable. Olsalazine (really, a prodrug double-5-ASA that, like sulfasalazine, required bacterial hydrolytic luminal cleavage of the azo bond) is believed to have a similar colonic metabolism with epithelial acetylation and fecal elimination. Balsalazide, also an azo-bond drug with aminobenzoyl-B-alanine as an inert carrier, was also demonstrated to be poorly absorbed from the colon so that the 5-ASA component was available there. Olsalazine, however, also had another property that limited its clinical effectiveness in some patients. This drug appeared to cause increased small intestinal secretion, particularly bicarbonate, and led to diarrhea.

For mesalamine, a number of formulations were devised with luminal release properties defined by a different form of pH-dependent capsule or carrier system (ie, Asacol, Salofalk, Mesasal, and Pentasa). As a result, each of these formulations had slightly different kinetics of drug delivery and location of action. With limited disease extent (ie, proctitis or proctosigmoiditis), rectally administered 5-ASA enemas or suppositories were usually sufficient. With more extensive disease or in those patients that find rectal therapies difficult, orally released forms of 5-ASA linked to an inert carrier were used. For most of these forms, different medicinal coatings were used to delay release of the active 5-ASA within the intestinal lumen. Other forms, such as Pentasa, incorporated mesalamine into ethylcellulose micro-granules so that mesalamine could be released in a pH-dependent fashion. For this Pentasa product, some release of the 5-ASA moiety occurred in the small intestine as well as the colon, which is believed by some clinicians treating patients with inflammatory bowel diseases to provide a therapeutic advantage if small intestinal inflammatory disease was present (eg, Crohn's disease).

A number of serious hypersensitivity-type adverse effects of aminosalicylates have also been recorded. These are less common than adverse effects of sulfasalazine and include pneumonitis, myopericarditis, hepatitis, pancreatitis. Recurrent myopericarditis may also develop, although this may be more likely related to recurrent disease flares.[22] In addition, nephritis may occur. Although there remains a concern for the potential for interstitial nephritis associated with 5-ASA use, particularly with the high dose ranges, significant dose- and treatment-duration dependent declines in the creatinine clearance has been noted after long-term 5-aminosalicylic acid treatment.[23] Finally, mesalamine can cause worsening of colitis, as can sulfasalazine,[24] in both oral and enema forms.[25,26] In some patients, this may be more evident as the dosage of other therapies, specifically corticosteroids, given in conjunction with 5-ASA, are tapered. In others, a true hypersensitivity form of colitis may occur, including hypersensitivity to topical 5-ASA agents.

In practical terms, 5-ASA products are used to induce remission in patients with mild to moderately

symptomatic distal or more extensive colitis. The drug is often used in conjunction with other agents including corticosteroids if more severe disease is present. There appears to be a dose response with increasing doses, generally in the 1 to 5 gram range. However, in symptomatically active disease, there is little evidence to support one particular 5-ASA product over another agent. In distal disease, use of local agents is preferred (eg, enemas or suppositories). For maintenance treatment, there is a benefit to continuous 5-ASA in distal or more extensive colitis. Recent studies suggest that multimatrix once daily dosing may be better, in part, because compliance by patients is presumably better (than multi-dosing through the day).

Author Contributions

Conceived and designed the experiments: HJF. Analysed the data: HJF. Wrote the first draft of the manuscript: HJF. Contributed to the writing of the manuscript: HJF. Agree with manuscript results and conclusions: HJF. Jointly developed the structure and arguments for the paper: HJF. Made critical revisions and approved final version: HJF. All authors reviewed and approved of the final manuscript.

Funding

Author(s) disclose no funding sources.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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