Review article

MEDICAL TREATMENT OF INFLAMMATORY BOWEL DISEASE (Part one)

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Abstract

Medical therapy of inflammatory bowel disease (IBD) can be considered in several subcategories, and this review is designed to provide selective updates for some of the most important therapeutic entities currently marketed or soon to be available for the medical management of IBD. Although conventional corticosteroids have been a major component of acute inflammatory bowel disease management, steroids have many serious disadvantages; and toxicity is heightened with chronic steroid therapy. Newer corticosteroids, particularly budesonide, may be less toxic than older agents such as prednisone. Budesonide may be used as delayed release tablets in Crohn's disease (CD) or as an enema in active distal ulcerative colitis (UC). The advances in therapy of CD and UC have been characterized mainly by the more extensive use of immunosuppression and aminosalicylic acids. Cyclosporin A (CSA) may become a drug of choice to treat severe UC, but its long-term effect is probably insufficient. Topically glucocorticosteroids (GCS) are hopeful in right ileocolonic UC. The most significant development in recent years is the introduction of immunomodulatory treatments by using cytokines and anticytokines. Immunomodulation therapy creates great expectations since early reset of the immunostat might be able to control inflammation in the long term. Current treatment strategies are anti-inflammatory and to modulate the immune response. Standard therapies with sulphasalazine (SAS) or 5-aminosalicylic acids (5-ASA, mesalazine or mesalamino), GCS and antibiotics yield a fair immediate success but long-term response to these therapies is poor. However, budesonide is not completely free from steroid side effects, and may share in some of the toxicity of older corticosteroids, particularly when high dose budesonide is administered. Topical and oral aminosalicylates are widely utilized for the treatment of mild to moderate active UC and mild active CD, and they also are efficacious for maintenance of IBD remission. Recent data

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continue to support the concept that higher doses and prolonged use of mesalamine-based drugs are therapeutically superior to lower doses and short term treatment. In addition, the combination of oral and rectal aminosalicylate formulations often succeeds in patients refractory to either used alone. The immunomodulatory drugs azathioprine and 6-mercaptopurine are particularly effective in treating both CD and UC, and methotrexate has also shown some promise in CD therapy. Immunosup-pressive therapy for inflammatory bowel disease initially met with strong physician resistance. However, views have shifted in response to positive data on the utility of immunosuppressive agents in many cases of IBD. Although cyclosporine may be used as a 'rescue' medication in some severe IBD cases, it has been associated with severe toxic reactions. Possible candidates for cyclosporine treatment should be offered such therapy only in academic centers highly experienced with the nuances of this modality. Clinical trials of the newer entities IL-10, IL-11, tacrolimus, and anti-TNFalpha, have demonstrated variable efficacy in refractory IBD patients. Anti-TNFalpha has been very impressive, particularly in the presence of fistulizing CD. Many physicians have utilized various antibiotics empirically as part of their 'general' management of IBD. Only metronidazole has been adequately studied in controlled CD

CD. Many physicians have utilized various antibiotics empirically as part of their 'general' management of IBD. Only metronidazole has been adequately studied in controlled CD trials, but other antibiotic studies are pending. Further exploration of antimicrobial treatment for IBD is clearly warranted. Many other investigational agents in disparate pharmaceutical categories have been employed in IBD therapy; and some of these also show varying degrees of promise, including the *Aloe vera* derivative acemannan, several formulations of heparin, and both transdermal and intra-rectal nicotine. Despite the growing list of medications and formulations promoted for the treatment of IBD, no single drug or recognized combination has yet been confirmed as dependably clinically effective. Many additional investigations of IBD medical therapy are needed, including permutations of conventional medications, along with newer agents that may be more precisely targeted to specific aspects of IBD pathophysiology. All physicians who care for UC and CD patients enthusiastically await more optimal regimens for these challenging disorders.

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Idiopathic inflammatory bowel disease consists of Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the gastrointestinal tract, from the mouth to the anus, and is also known as regional enteritis, terminal ileitis, or granulomatous colitis. UC is limited to the colon and rectal involvement is present for 95% of the time. Ten percent to fifteen percent of patients with irritable bowel syndrome cannot be clearly defined as having either CD or UC and are termed indeterminate colitis [1]. CD and UC are probably syndromes rather than single indeterminate colitis [1]. CD and UC are probably syndromes rather than single entities. Neither the susceptibility genes nor definite environmental factors have been found thus far. The "immune concept" of these disorders might not include all patients. Consequently immune-based new approaches on alternative etiological/ pathophysio-logical pathways may be necessary. New developments in diagnostic techniques will probably improve patient acceptance and may even help to prevent carcinoma development. Newer drugs and recent studies on all agents have resulted in a more defined approach based specifically

drugs and recent studies on all agents have resulted in a more defined approach based specifically on the patient's condition [2-4].

The term inflammatory bowel disease traditionally comprises CD and UC, an inter-mediate variant of the two major forms [3,5-8]. The term is commonly used, in the literature and in clinical practice even though it has never been revised in a Consensus Conference. The present nosology of inflammatory bowel disease seems not to be entirely satisfactory as it is limited to chronic diseases only and does not include several recently described idiopathic inflammatory bowel disorders. Although the aetiology of inflammatory bowel disease remains unknown, both CD and UC are characterized by a similar pathogenesis that consists in a persistent intestinal inflammation resulting from disregulation of the gut mucosal immune system. The pathogenetic mechanisms could, therefore, provide a suitable criterion for the classification of idiopathic inflammatory bowel disease. A revised classification of inflammatory bowel disease is thus proposed. It seems reasonable to subclassify inflammatory bowel disease into acute and chronic forms. Acute forms should include the sudden attacks of CD and UC with rapid and complete resolution and the so-called "acute self-limited colitis". The chronic forms should comprise, besides the classical forms of CD, UC and indeterminate colitis, also other idiopathic inflammatory bowel conditions such as collagenous colitis, lymphocytic colitis and eosinophilic gastroenteritis. Patients with an inflammatory bowel disease, such as CD or DC, have recurrent symptoms with considerable morbidity [7-10]. Patient involvement and education are necessary components of effective management. Mild disease requires only symptomatic relief and dietary manipulation. Mild to moderate disease can be managed with 5-aminosalicylic acid compounds, including olsalazine and / mesalamine. Mesalamine enemas and suppositories are useful in treating proctosigmoiditis [5,ll]. Antibiotics such as metronidazole may be required in patients with CD. Corticosteroids are beneficial in patients with more severe symptoms, but side effects limit their use, particularly for chronic therapy. Immuno-suppressant therapy may be considered in patients with refractory disease that is not amenable to surgery. Inflammatory bowel disease in pregnant women can be managed with 5-aminosalicylic acid compounds and corticosteroids. Since longstanding inflammatory bowel disease (especially UC) is associated with an increased risk of colon cancer, periodic colonoscopy is warranted.

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The advances in therapy of CD and UC have been characterized mainly by the more extensive use of immunosuppression and aminosalicylic acids [12]. Cyclosporin A (CSA) may become a drug of choice to treat severe UC, but its long-term effect is probably insufficient. Topically glucocorticosteroids (GCS) are hopeful in right ileocolonic UC, but no action for maintenance therapy [4-6]. The most significant development in recent years is the introduction of immunomodulatory treatments by using cytokines and anticytokines. Immunomodulation therapy creates great expectations since early reset of the immunostat might be able to control inflammation in the long term. Current treatment strategies are anti-inflammatory and to modulate the immune response. Standard therapies with sulphasalazine (SAS) or 5-aminosalicylic acids (5-ASA, mesalazine or mesalamine), GCS and antibiotics yield a fair immediate success but long-term response to these therapies is poor. The greatest advance has been the introduction of immuno-suppressive strategies [4-11]. The indexes like the clinical activity index (CAI) proposed by Kruis W et al [13]. High dose balsalazide (3.0 g twice daily) was superior in maintaining remission in patients with ulcerative colitis compared with a low dose (1.5 g twice daily) or a standard dose of mesalazine (0.5 g three times daily). All three treatments were safe and well tolerated.

In most patients coming to the general practitioner or specialist with a history of bloody diarrhea, bacteria or drugs are the most likely causative agents and it will be possible to make a diagnosis fairly easily. Because of differences in treatment, CD and UC must however seriously be considered especially in younger patients, with severe symptoms and whenever the history is prolonged. A variety of colitides may indeed be clinically confused with CD and UC. Pathological mimics that should not be missed include infectious diseases such as Campylobacter colitis, yersiniosis, amoebiasis and others; drug-induced diseases (due to nonsteroidal antiinflammatory drugs); diverticular disease-associated colitis; intestinal endometriosis; intestinal vasculitis and Behcet's disease and iatrogenic conditions such as graft-versus-host-disease and radiation colitis. In most situations a precise diagnosis of these conditions should be possible when all data

diverticular disease-associated colitis; intestinal endometriosis; intestinal vasculitis and Behcet's disease and iatrogenic conditions such as graft-versus-host-disease and radiation colitis. In most situations a precise diagnosis of these conditions should be possible when all data are available. The term "indeterminate colitis" is used, when a diagnosis of chronic idiopathic IBD is suggested, but the differential diagnosis between CD and UC can not be solved. This occurs in approximately 5% of all patients with IBD. Diagnostic problems can occur in acute fulminant colitis, acute prolonged colitis, chronic relapsing disease and pouchitis. Indeterminate colitis is essentially a temporary diagnosis. Surgical and medical treatment of these patients can be difficult. When surgical treatment is indicated, the type of surgery must be seriously considered. The clinical course of patients with indeterminate colitis is usually more severe when compared with classical UC and these patients require often more severe medical treatment. Diagnostic problems can also arise in longstanding IBD (CD or UC). Relapse of symptoms can be due to intercurrent infection (CMV is one of the candidates). Medical treatment can influence the microscopic features and induce a discontinuous inflammation in UC, reminiscent of CD. In cases of doubt, the original biopsies should be reviewed to ascertain the diagnosis, and orient treatment [14].

Current treatment of Crohn's disease and ulcerative colitis

Since its synthesis in the 1930s and subsequent introduction, sulfasalazine has been an effective treatment for inflammatory bowel disease. However, up to one-third of patients are unable to take the drug because of severe intolerance. The finding in 1977 that the anticolitic effect of sulfasalazine lay in its 5-aminosalicylic [(5-ASA); mesalazine] moiety led to the development of new generations of 5-ASA agents. These new agents include a slow continuous release formulation, pH-dependent release formulations, formulations using alternative carrier molecules and rectally administered formulations. Newer 5-ASA formulations are more effective than placebo in maintaining remission of ulcerative colitis. They have also been used for the treatment of active CD as well as maintenance treatment of ileocolonic CD, although their role in isolated small bowel disease is controversial. In general terms, all of the newer 5-ASA preparations are much better tolerated than sulfasalazine. The use of standard dosages of mesalazine in pregnancy appears to be tolerated; however, continuing surveillance of pregnancy outcome is recommended. While there is evidence that mesalazine can cause nephrotoxic reactions, these reactions can occur with all 5-ASA-containing preparations, particularly in individuals with existing renal disease. Blood dyscrasias can also occur with all aminosalicylates. Corticosteroids and the 5-aminosalicylate (5-ASA) drugs still constitute the mainstays of therapy, with azatioprine/mercaptopurine an established second-line agent for resistant disease. Primarily nutritional therapy has a place for some patients with CD, and alternative immunosupressants are finding their own disease. The medical management of inflammatory bowel diseases is poised to enter to new era if the current promise shown by investigatory immunomodulatory regimes translates into confirmed effective therapy.

Despite conventional medical and/or surgical intervention, endoscopic and symptomatic relapse is common among individuals with CD. Treatment goals have therefore been refocused to include achieving control of active disease and maintaining remission with agents associated with a minimum of toxic adverse effects. Conventional treatment regimens have been used with varying success in regard to these therapeutic goals. Traditionally, aminosalicylates have been considered effective in inducing a response in some patients with mild-to-moderate CD but have demonstrated little or no long-term benefit in controlled clinical trials. Glucocorticosteroid therapy is associated with higher rates of response in patients with active CD; however, clinical benefits are frequently off set by the common occurrence of corticosteroid-related toxicity. Oral controlled-release budesonide has demonstrated comparable efficacy to prednisolone with less risk for adverse effects, although many questions remain regarding the long-term use of this agent. Response to standard immunosuppressive agents such as azathioprine and 6-mercaptopurine in patients with active disease may require 3 to 6 months from initiation of treatment. These agents are therefore considered most valuable as maintenance therapy, providing consistent long-term benefit in patients with chronic refractory or

corticosteroid-dependent disease. Although the incidence of allergic adverse effects is relatively low with azathioprine/6-mercaptopurine, more serious adverse effects, including bone marrow suppression, hepatotoxicity, pancreatitis, and infectious complications, can occur. Limited success in the treatment of perianal disease has been achieved with antibiotics such as metronidazole and the immunosuppressives cyclosporine and azathioprine/6-mercaptopurine. Although broader use of immunosuppressive agents has allowed improvement in the maintenance of remission in patients with CD, long-term safety data with these agents are lacking, concerns about toxicity and the potential risk for neoplasia remain, and attenuation of response with chronic immunosuppressive use can occur. Therefore, innovative therapeutic approaches are needed to meet key treatment goals often not addressed by conventional therapies [14,15].

Ulcerative colitis (UC) is a mucosal disease and therefore well suits for treatment in most instances with topically acting drugs at the level of the colonic mucosa. UC is controlled mainly by using GCS and 5-ASA [14-16]. Ardizzone et al [16] had reviewed the role of corticosteroids, ASA and mesalazine (5-ASA, mesalamine), immunosuppressive agents and alternative novel drugs for the treatment of distal UC. Short cycles of traditional, rectally administered corticosteroids (methylprednisolone, betamethasone, and hydrocortisone) are effective for the treatment of mild to moderately active distal UC. In this context, their systemic administration is limited to patients who are refractory to either oral 5-ASA, topical mesalazine or topical corticosteroids. Of no value in maintaining remission, the long-term use of either systemic or topical corticosteroids may be hazardous. A new class of topically acting corticosteroids [budesonide, fluticasone, beclomethasone dipropionate, prednisolone-21-methasulphobenzoate, tixocortol (tixocortol pivalate)] represents a valid alternative for the treatment of active UC, and may be useful for refractory distal UC. Although there is controversy concerning dosage or duration of therapy, oral and topical mesalazine is effective in the treatment of mild to moderately active distal UC. Sulfasalazine and mesalazine remain the first-choice drugs for the maintenance therapy of distal UC. Evidence shows a trend to a higher remission rate with higher doses of oral mesalazine. Topical mesalazine (suppositories or enemas) is also effective in maintenance treatment. For patients with chronically active or corticosteroid-dependent disease, azathioprine and mercaptopurine are effective in reducing either the need for corticosteroids or clinical relapses. Moreover, they are effective for long-term maintenance remission. CSA may be useful in inducing remission in patients with acutely severe disease that does not achieve remission with an intensive intravenous regimen. Existing data suggest that azathioprine and mercaptopurine may be effective in prolonging remission in these patients. The role of alternative drugs in the treatment of distal UC and its different forms is reviewed. In particular data are reported concerning the effectiveness of 5-lipoxygenase inhibitors, topical use of short chain fatty acids, nicotine, local anesthetics, bismuth subsalicylate enema, sucralfate, clonidine, free radical scavengers, heparin and hydroxychloroquine. The management of patients with acute severe UC requires careful in-hospital assessment of the patient and the coordinated treatment of a team of experienced gastroenterologists and surgeons. Complete understanding of the potential complications and their management, especially toxic megacolon, is essential.

The current medical arsenal and advocate a standardized approach to management that includes continuous, high dose iv hydrocortisone, more aggressive use of topical steroids as well as feeding the patients and continuing (but not initiating) oral 5-ASA agents was reviewed[5]. For those patients whose disease proves refractory to iv steroids, iv. CSA (with an acute response rate of 82%) is an essential component in the medical management of these patients. Antibiotics should be used only when specifically indicated. Total parental nutrition has not been shown to be helpful in the acute setting. Air contrast barium enema and colonoscopy have been used to predict response but may be dangerous diagnostic modalities in these acutely ill patients and are not better than good clinical judgement. Marion et al[17] reviewed and advocate long-term management of acute response using 6-mercaptopurine or azathioprine. The surgical experience and the postoperative complications of the ileal pouch anal anastomosis,

which include acute pouchitis in 50%-60%, chronic pouchitis in 5%-10% and recent reports of dysphasia among patients with chronic pouchitis, must be considered before colectomy is advised. Over 80% of patients with acute severe colitis can be spared colectomy using the current arsenal of medical therapies [7-10].

The inhibited release of 5-lipoxygenase products may account for some of the anti-inflammatory effects of ropivacaine seen in the treatment of DC [18]. Prompt diagnosis and exclusion of infection requires a minimum of rigid sigmoidoscopy, rectal mucosal biopsy and stool culture. Admission to hospital is mandatory for patients with features of severe disease, or who are in their first attack ofUC and have bloody diarrhea, even if the criteria for severe disease are not met. Once admitted, plain abdominal X-ray, full blood count, and serum albumin and C reactive protein should be used to monitor the patients on alternate days; temperature and pulse rate should be recorded four times per daily. Treatment should be instituted as soon as the diagnosis is made with an intravenous corticosteroid (hydrocortisone 100 mg iv, four times daily or equivalent). Antibiotics may be included if infection cannot be confidently excluded. Free diet is allowed but attention should be given to nutritional, fluid and electrolyte status with intravenous replacement if necessary. Any evidence of colonic dilatation occurring despite maximal therapy should be regarded as an absolute indication for colectomy. The patient should be kept fully informed from an early stage about the likely natural history of the condition and about the possible therapeutic options including surgery. CSA therapy should be reserved for patients who have a poor response to the first 3d-4d of corticosteroid therapy, particularly those with serum C reactive protein > 45 mg/L and who do not yet have absolute indications for colectomy. Most patients who have not convincingly responded within 10 day of starting medical therapy should undergo colectomy, although some responders who are febrile may reasonably continue for up to 14 days before a final decision. Approximately 30%-40% of patients with severe colitis will need colectomy within the first 6 months. With optimal management, mortality can be zero, but better medical therapies are urgently needed to reduce the colectomy rate [19].

Finnie et al [20] speculated that corticosteroids might cause beneficial stimulation of mucus synthesis, since this is a known action of carbenoxolone, a corticosteroid itself, and has also been proposed as a possible mechanism for the protective effect of smoking on UC. We have therefore compared the effects of corticosteroids including carbenoxolone, and nicotine on mucin synthesis, assessed by incorporation of N-[3H] acetylglucosamine into mucin by colonic epithelial biopsies in culture. In histologically normal biopsies from the left colon, hydrocortisone and prednisolone caused a very marked concentration-dependent increase in mucin synthesis, with maximal effect at 6 nmol/L ($P < 0.001$) and 1.5 nmol/L ($P < 0.001$) respectively. The maximal effect of hydrocortisone was significantly greater than that of prednisolone ($P < 0.05$). Carbenoxolone, 0.17 mmol/L, also increased mucin synthesis in the left colon [$P < 0.05$, $n = 15$ (three patients)]. In contrast, these corticosteroids caused only a small, non-significant increase in mucin synthesis in the histologically normal right colon; fludrocortisone, 2 nmol/L and 20 nmol/L, and aldosterone, 0.1 nmol/L-10 nmol/L had no effect. Nicotine significantly increased mucin synthesis between 62.5 nmol/L and 6.25 nmol/L ($P<0.05$ at all concentrations) in both the right and left colon. In biopsies from the relatively uninvolved right colon of patients with UC, corticosteroids and nicotine caused relatively smaller increases in mucin synthesis. The marked stimulation of mucin synthesis by corticosteroids suggests that this may account, at least in part, for their therapeutic effect in UC [14].

The current medical therapy of severe, acute ulcerative colitis is reviewed. The role and of 5-ASA, corticosteroids, immunosuppressive agents and surgery are outlined. A systematic approach using a combination of these agents to induce a remission is presented. A model for long term maintenance therapy following a response in the acute setting to avoid steroid dependence and surgery is proposed. The role of surgery in ulcerative colitis should be limited to patients who either fail medical therapy or in whom dysplasia or cancer has been detected. A realistic assessment of the potential pitfalls of surgical intervention, such as ileal pouch-anal anastomosis, is discussed [21].

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