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EDITORIAL

Recent advances in the management of distal ulcerative colitis

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Abstract

The most frequent localization of ulcerative colitis (UC) is the distal colon. In treating patients with active distal UC, efficacy and targeting of the drug to the distal colon are key priorities. Oral and rectal 5-aminosalicylic acid (5-ASA) preparations represent the first line therapy of mild-to-moderate distal UC for both induction and maintenance treatment. It has been reported that many UC patients are not adherent to therapy and that non-compliant patients had a 5-fold risk of experiencing a relapse. These findings led to the introduction of once-daily oral regimens of 5-ASA as better therapeutic options in clinical practice due to improved adherence. New formulations of mesalazine, including the multi-matrix delivery system, and mesalazine granules, which allow once-daily administration, have been developed. They have been demonstrated to be efficacious in inducing and maintaining remission in mild-to-moderate distal UC in large clinical trials. However, existing data for distal UC are rather insufficient to make a comparison between new and classical 5-ASA formulations. It seems that the new formulations are at least as effective as classical oral 5-ASA formulations. Other treatment options, in the case that 5-ASA therapy is not effective, include systemic corticosteroids, thiopurines (azathioprine or 6-mercaptopurine), cyclosporine, infliximab and surgery. The combination of a prompt diagnostic work-up, a correct therapeutic approach and an appropriate follow-up schedule is important in the management of patients with distal UC. This approach can shorten the duration of symptoms, induce a prolonged remission, improve patient's quality of life, and optimize the use of health resources.

Key words: Aminosalicylates; Azathioprine; Infliximab mesalazine; Ulcerative colitis

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INTRODUCTION

The majority of newly diagnosed adult patients with ulcerative colitis (UC) present with disease limited to the distal or left side of the colon[1], which is also called distal UC. The term "distal UC", therefore, defines disease distal to the splenic flexure, which includes proctitis (involvement of rectum only), proctosigmoiditis (involvement of rectum and sigmoid colon) and left-sided colitis (involvement extending as far as the descending colon or splenic flexure). Cases with proctitis (E1) and left sided colitis (E2), according to the recent Montreal classification[2], are included. Approximately 80% of UC patients present as distal UC and about 20% present with extensive colitis or pancolitis[1]. The literature suggests that the course of distal UC varies. Its onset may be gradual or abrupt, and most patients experience remitting and relapsing symptoms.

As for all cases of inflammatory bowel disease, the aim of medical management of patients with distal UC is to induce remission in active disease and to minimize the risk of relapse. In treating active distal UC, efficacy and targeting of the drug to the distal colon are key priorities. Moreover, for maintenance therapy, long-term toxicity and factors that affect compliance are important. Treatment options include 5-aminosalicylic acid (5-ASA and derivatives), corticosteroids and immunosuppressive therapy. Emerging data suggest that early, aggressive treatment of distal UC may prevent or delay proximal extension, an occurrence that otherwise is common[3].

The main recent advances in conventional therapy for distal UC are once-daily mesalazine therapy, the new delivery system utilizing Multi Matrix System (MMX) technology, the newly developed micropellet formulations of 5-ASA and the reappraisal of high-dose mesalazine and immunomodulators. Especially the recent introduction of novel 5-ASAs provides a wider choice to clinicians of oral therapy for UC patients.

5-ASA is the standard first-line treatment for mild-to-moderate distal UC. Since 5-ASA is believed to act topically, the development of 5-ASA formulations aim to minimize the systemic absorption of 5-ASA from the small intestine and to maximize the delivery of the active drug to the site of inflammation in the colon. Various rectal gels, liquids, and foam enemas have been developed and fulfil these criteria by delivering 5-ASA directly to the site of inflammation, while ensuring minimal systemic absorption. However, these formulations are often associated with adverse events, such as leakage and abdominal bloating. Moreover, many patients find rectal formulations impractical and, as a result, compliance with prescribed dosing regimens is poor. Consequently, rectal formulations are mainly used as add-on therapy[4].

Only 40%-60% of the patients who are newly diagnosed or have longstanding disease are adherent to therapy[5]. It was shown that non-compliant patients had a 5-fold risk of experiencing a relapse as compared to patients taking more than 80% of their prescribed mesalazine medication[6].

Treatment alternatives to 5-ASAs include other topical preparations for rectal administration and oral and intravenous therapies.

This review discusses recent clinical trials pertaining to the management of distal UC. It summarizes the evidence for recent developments in the use of established therapies, as well as emerging novel therapies.

TREATMENT OF THE ACUTE PHASE

Several medications are available for the treatment of the acute phase of distal UC. Oral formulations and topical therapies with aminosalicylates or corticosteroids have shown to be highly effective in this situation. Meta-analysis of the published data and important relative reviews have been published[4,7-10].

In patients with mild-to-moderately active ulcerative proctitis, rectal administration of suppositories of 5-ASA or corticosteroids has been established as first-line therapies. In this setting, suppositories of 5-ASA are more effective than rectal steroids and has been shown to be more effective than oral 5-ASA[11].

Patients with active distal UC can be treated with rectal 5-ASA (enemas, foams, or suppositories), oral 5-ASA, or a combination of both. Several controlled trials have shown that rectal therapies have a more rapid effect than oral treatment[12,13]. Meta-analysis of the published data showed that rectal 5-ASA is superior to placebo and to conventional rectal corticosteroids for inducing remission of symptoms, endoscopy, and histology of distal UC[7]. Moreover, it has been found that the combination of oral and rectal 5-ASA further improves the efficacy and speed of improvement in patients with distal UC without differences in safety[13].

Although a dose response of oral mesalazine for active UC has been suggested, the benefit of mesalamine 4.8 g/d over 2.4 g/d is limited to symptom improvement rather than remission of the disease[10]. The ASCEND Ⅱ trial suggested that 4.8 g is superior to 2.4 g in patients with moderately active UC[14]. However, other recent studies do not suggest a difference[10].

There is evidence that distal active UC of mild-moderate severity should initially be treated with a combination of topical aminosalicylates and oral mesalazine ($\geqslant$ 2 g/d). Concerning topical treatment alone, steroids or mesalazine are also effective, but mesalazine is more effective than steroids. Each one, as well as oral aminosalicylates alone, is less effective than combination therapy[15]. The response to oral and rectal therapy should be apparent in about 2 wk and, if rectal bleeding persists, then the response is slow and steroid therapy should continue.

In the case that rectal 5-ASA or corticosteroids and oral 5-ASA therapy are not effective, then oral corticosteroids should be administered. Usually, the suggested dose of oral prednisone (or equivalent) is 40 mg daily, which leads to rapid clinical response in the majority of patients[9]. After a clinical response, prednisone is tapered (5 mg to 10 mg/1-2 wk) with the rate of tapering depending on the disease severity and rapidity of improvement. At the same time, oral and rectally administered 5-ASA therapy should be continued with the goal of maintaining remission of UC once prednisone is discontinued.

Patients with severe distal UC should be hospitalized and treated with IV corticosteroids. Another option in these cases is the use of infliximab. Systemic corticosteroids are appropriate if symptoms of active distal UC do not respond rapidly to mesalazine. Severe distal UC is usually an indication for hospitalization for intensive treatment with systemic administration of the therapy[15]. Treatment with corticosteroids intravenously is evaluated after about 5 d.

In cases with moderate-to-severe active disease who have failed therapy with aminosalicylates, corticosteroids, or immunomodulators, the administration of infliximab is indicated. The evidence for this is provided from two large randomized, double-blind, controlled trials: ACT-1

and ACT-2 where 56% of the patients had left-sided or distal UC suggesting that infliximab is effective in this group of patients[16]. However, it should be realized that the steroid-free remission rate after 7 mo (30 wk) on infliximab is only 21%[16]. Furthermore, infliximab seems to be effective as a rescue therapy to avoid colectomy in severe UC unresponsive to intravenous steroids in short-term and long-term follow-up[17,18]. The role of infliximab in cases with severe distal UC that are resistant to therapy, and whether it is an alternative to surgery, remains to be established.

MAINTENANCE TREATMENT

All patients with distal UC are at risk for relapse and should receive maintenance treatment. The vast majority of untreated patients will relapse by 1 year, whereas maintenance therapy significantly decreases the risk of relapse[9]. Therefore, long-term treatment is indicated for reduction of the risk of relapse, but also for decrease of proximal extension of the disease and for reduction in the development of carcinoma. Only a few cases with mild ulcerative proctitis do not require maintenance treatment.

The choice of the appropriate maintenance therapy for a patient with distal UC should be based on the efficacy of the medication in combination with its long-term safety, tolerability, convenience and acceptability to the patient.

The mainstay of maintenance therapy for distal UC has been 5-ASA for the past few decades. Rectally administered 5-ASA preparations are effective for maintenance of remission in most patients with distal UC. The combination of rectal and oral 5-ASA may be the most effective strategy. However, rectal formulations are often associated with undesirable side effects (leakage and abdominal bloating), and many patients find them impractical and compliance with this treatment is poor. Therefore, long-term 5-ASA for oral maintenance treatment of distal UC is usually preferred by patients and doctors. It is of note that using 5-ASA therapy for maintaining remission after patients required prednisone is a common practice, but it is not based on the literature.

The dose-response of 5-ASA formulations in maintenance therapy of distal UC has not been definitively evaluated.

Where 5-ASA has insufficient efficacy, immune modulation is indicated. Thiopurines (azathioprine and 6-mercaptopurine) have been found to be superior to placebo in maintaining remission in distal UC[19,20]. Overall, oral therapy with azathioprine or 6-mercaptopurine is reserved for patients with steroid-dependent distal UC and those with chronic disease that is refractory to other drugs. Patients with early stage disease have higher steroid-free remission rates on azathioprine compared to patients with late stage disease[21]. Moreover, it has been suggested that increasing the dose of azathioprine up to 2.5 mg/kg appeared beneficial in patients who had not responded to 2 mg/kg per day[20].

The use of azathioprine in distal UC is less indicated than in extensive UC. Moreover, the relapse rate after drug withdrawal is significantly lower in distal UC compared to extensive UC[22]. A recent meta-analysis showed that thiopurine drugs are more effective than placebo for the prevention of relapse in UC, with a number needed to treat of 5 and an absolute risk reduction of 23%[23].

Methotrexate has also been used to maintain remission in patients with steroid-dependent UC who fail to respond to or who are intolerant of thiopurines, but the evidence is mainly based on uncontrolled studies with small sample sizes and heterogeneous doses[24,25]. In a recent study, clinical response to methotrexate was seen in 7 of 9 (78%) of UC patients who were refractory to thiopurines and 15 of 23 (65%) who were intolerant to thiopurines[26]. However, the data are limited and evidence is lacking to recommend methotrexate to maintain remission in UC.

REFRACTORY DISTAL UC

Refractory distal UC is a term with different definitions, but the most accepted is that of the case who failed or has partial therapeutic response to conventional therapy. A patient with refractory distal UC requires a complete evaluation of possible exogenous and endogenous factors contributing to this refractory condition. Enteric infections, such as clostridium difficile, campylobacter jejuni, salmonella, shigella, cytomegalovirus, herpes simplex virus and various parasitic infections, should be excluded. It is of note that the prevalence and case fatality of UC patients complicated by clostridium difficile infection rose significantly during last few years[27].

Moreover, other reasons for refractoriness include poor adherence with therapy, inadequate concentrations of the active drug, unrecognised complications (such as proximal constipation) or inappropriate diagnosis (such as co-existent irritable bowel syndrome, Crohn's disease, mucosal prolapse, or very rarely, cancer)[15]. Medication history should be obtained in detail since some agents, specifically nonsteroidal anti-inflammatory drugs and antibiotics, may play a role in the activity of the disease.

Another parameter that should be taken into account is approximately half of the patients with proctitis or distal UC present with progression of the disease and this possibility should be examined in cases that present with refractoriness. Moreover, possible worsening of the symptoms by 5-ASA preparations, although rare, should be kept in mind and, in this case, aminosalicylates should be discontinued.

Patients with distal UC not responding to rectal and/or oral 5-ASA or corticosteroids present a treatment dilemma. Options for therapy for these refractory patients include infliximab and cyclosporine. Infliximab 5 mg/kg induction (0, 2 and 6 wk) followed by maintenance therapy (every 8 wk) offers an effective treatment option for patients with refractory distal UC. The use of infliximab has also been found to be effective in preventing colecto-

my in some cases with refractory UC[17,18], but in cases that are finally operated on, it seems that there are increases in the risk of short-term postoperative complications. This is supported by the findings of a recent meta-analysis[28].

Intravenous cyclosporine (2-4 mg/kg per Id) is effective in refractory patients with distal UC but is associated with rare and potentially life-threatening side effects, such as nephrotoxicity, opportunistic infections, and seizures. Patients who respond to cyclosporine require azathioprine or 6-mercaptopurine for maintenance of remission[9].

In severe refractory distal UC not responding to intensive treatment, or if the symptoms of the disease have major adverse effects on a patient's quality of life, surgery should be considered. Overall, patients with distal UC are less likely to require surgery than patients with extensive UC. Among patients who have a colectomy for refractory UC, 10%-35% are reported to have distal disease[29,30].

NEW ORAL MESALAZINE FORMULATIONS

The most important aim of treatment for UC with 5-ASA is to deliver high concentrations of the drug topically to areas with active inflammation. Various formulations have been developed to enable release of orally administered 5-ASA in the colon.

Commercially available 5-ASA includes azo-bond prodrugs, such as sulfasalazine, olsalazine and balsalazide, and delayed and controlled-release forms of mesalazine. Although emphasis has been placed on the manner in which different delivery systems may influence responses to 5-ASAs, the evidence in clinical practice for variability in efficacy among these products is rather weak.

Two major problems have appeared during the last decades with the use of oral 5-ASA in UC patients. The first is that azo-bonded and delayed-release formulations may not deliver therapeutically effective doses of 5-ASA to the left colon. There is evidence from clinical studies showing mucosal 5-ASA concentrations using azo-bonded or bolus-release formulations to be highest in the right colon, whereas in the rectum, the concentration of 5-ASA is significantly lower[31,32]. The second is that these formulations were given multiple times daily since this has been considered essential to ensure that therapeutically effective 5-ASA doses are maintained in the colon. This approach has been shown to be efficacious for the treatment of UC in clinical studies, but patient compliance has been demonstrated to be poor in clinical practice, with the result of reduced drug efficacy and poorer disease control[6]. Therefore, the once-daily oral formulations of 5-ASA have been suggested as a better therapeutic option in clinical practice due to improved adherence.

Concerning safety, the majority of oral 5-ASA agents have safety profiles similar to that of a placebo in large clinical trials. Only sulfasalazine is not well tolerated since it is associated with dose-related side effects including nausea, vomiting, dyspepsia, anorexia, and headache.

There are no definitive data suggesting that one 5-ASA preparation is superior to another. The choice of 5-ASA agent for treatment of a patient with distal UC should be based upon tolerability, ability to titrate dose to effect and cost.

New mesalazine formulations have been developed with the aim of both increasing the adherence to oral mesalazine treatment and avoiding topical administration of the drug.

MMX mesalazine

The recently developed MMX technology (in Italy by Cosmo S.p.A. Corp) involves incorporating mesalazine into a lipophilic matrix that is itself dispersed within a hydrophilic matrix to delay and prolong dissolution. There is a gastroresistant polymer film that prevents initial drug release until exposed to a pH of 7 or higher, so the film coat normally starts to dissolve only in the terminal ileum. In this case the hydrophilic matrix is exposed to intestinal fluids and swells, leading to the formation of a viscous gel mass with a slow and gradual release of mesalazine throughout the length of the colon[33].

Initially, the efficacy of MMX mesalazine was compared with mesalazine enema in patients with left-sided active UC. Clinical remission occurred in 60% of patients in the MMX group and in 50% of the enema group. Similar improvement was seen in the endoscopic and histological pattern. In addition, the adherence rate in remission was 92% in the MMX group and 65% in the enema group[34].

In a large randomized, double-blind, placebo-controlled trial, Lichtenstein *et al*[35] investigated the efficacy of MMX mesalazine 1.2 g twice daily and 4.8 g once-daily compared with a placebo for 8 wk, for the induction of remission in patients with mild-to moderate UC. Both MMX mesalazine groups achieved statistically significant clinical and endoscopic remission compared with the placebo (34.1% and 29.2% *vs* 12.9%, 2.4 g/d and 4.8 g/d *vs* placebo, $P < 0.001$ and $P = 0.009$, respectively). Another large double-blind, placebo-controlled, multicenter clinical trial, by Kamm *et al*[36] randomized patients with active, mild-to-moderate UC to receive MMX mesalazine 2.4 g once daily, MMX mesalazine 4.8 g once daily, placebo, or a delayed-release (EUDRAGIT S-coated) mesalazine 800 mg 3 times daily. Significantly more patients achieved clinical and endoscopic remission at week eight in the MMX mesalazine groups compared with the placebo group (40.5% and 41.2% *vs* 22.1% with 2.4 g/d, 4.8 g/d *vs* placebo; $P = 0.01$ and $P = 0.007$). In contrast, the group of delayed-release mesalazine demonstrated only a trend for improvement (32.6% *vs* 22.1%, $P = 0.124$). It is of note that, in the subgroup analysis, no significant difference in the remission rates between extensive and left-sided colitis was found in the four groups of this study.

The efficacy of MMX mesalazine as maintenance therapy was examined in a more recent multicenter study[37]. Patients with UC were randomized to receive MMX mesalazine 2.4 g/d once daily, or delayed-release (EUDRAGIT S-coated) mesalazine 2.4 g/d twice daily, administered in a double-dummy fashion for 12 mo. All

patients were in remission with at least one documented relapse in the previous year. The data from this study indicate that MMX mesalazine 2.4 g/d once daily and delayed-release mesalazine 2.4 g/d twice daily are similarly tolerated and effective in the maintenance of remission of distal UC. However, when only the Italian population was examined, statistically significant treatment differences favouring MMX mesalazine were revealed.

In theory, once-daily dosing with MMX mesalazine may improve patient compliance and have higher remission rates than delayed-release mesalazine in the treatment of patients with distal UC. In order to confirm this theory, future studies evaluating compliance rates in clinical practice and larger studies focused on distal UC are required.

Mesalazine granules

Another new formulation of 5-ASA, which is becoming more widespread, is the micropellet release system, which allows once daily dosing in an easy-to-swallow formulation. It is provided as individual sachets containing a single dose, using granules to effect a delayed and sustained release of 5-ASA with similar delivery properties and systemic exposure to tablets.

Mesalazine granules are a multiparticulate formulation with an enteric acid-resistant film coating. Their dissolution starts approximately at pH > 6.0, leading to a delayed and, due to the inner polymer matrix, prolonged release of the active ingredient throughout the entire colon[38].

The mesalazine micropellet formulation was found to be as effective as tablets (EUDRAGIT L-coated mesalazine) in patients with mild-to-moderate UC, enabling a larger dose to be taken comfortably and conveniently with possible impact on patient compliance[39].

In a recent study, the administration of a 3 g once-daily dose of mesalazine granules was found at least as effective as a divided dose of 1 g given three times daily, leading a substantial proportion of patients with mild-to-moderate active UC into clinical and endoscopic remission. Especially for patients with distal UC, the clinical remission rate was significantly higher in the group using a once-daily dose compared to a three times daily dose (86% *vs* 73%, $P = 0.03$)[40].

In another recent study, after 1 year of treatment, 70.9% of the group given 2 g mesalazine granules once daily remained in remission *vs* 58.9% of the group given 1 g mesalazine granules twice daily; this difference was statistically significant ($P = 0.024$), indicating the increased efficacy of once daily, compared with twice daily, dosing[41].

These findings suggest that once daily treatment with mesalazine granules could be offered as a first choice of induction or maintenance treatment for UC patients.

OTHER NEW MEDICATIONS

Probiotics

VSL#3, a probiotic preparation containing 8 different bacterial strains, has been found to be effective in inducing remission of mild-to-moderate active UC, as well as in maintaining remission[42,43]. Concerning maintenance treatment of UC, *E. coli* Nissle 1917 has been found to be equivalent to mesalazine in maintaining remission in UC, including patients who were treated after an acute episode of UC[44]. The conclusion of a Cochrane review of randomized, controlled trials of probiotics in UC was probiotics added to standard therapy may provide modest benefits in the reduction of disease activity in patients with mild-to-moderately active UC[45].

Beclomethasone diproprionate

Recently, steroids with a colonic release mechanism and low systemic bioavailability, such as beclomethasone diproprionate are becoming available. Oral beclomethasone diproprionate in combination with oral 5-ASA has been found to be significantly more effective than 5-ASA alone in the treatment of patients with extensive or left-sided active UC[46]. In another large study of patients with active left-sided or extensive colitis, beclomethasone diproprionate 5 mg/d had an effect similar to that of mesalazine, but without systemic steroid side-effects[47]. Beclomethasone diproprionate has also been used in an enema with comparable tolerability and efficacy to mesalazine enema in mild active distal UC[48].

Budesonide MMX

The available oral formulations of budesonide have mainly been developed to treat ileocolonic Crohn's disease and not distal colonic lesions, due to their characteristic pattern of drug release in the gut. Budesonide enema is both effective and safe for the treatment of active distal UC[49]. Recently, a budesonide-MMX 9 mg formulation was developed and investigated in patients with UC. In a pilot study, budesonide-MMX induced a fast and significant clinical improvement in active left-sided UC without suppression of adrenocortical functions and without toxicity[50].

Adalimumab

Adalimumab is an anti-TNF agent similar to infliximab, but administered subcutaneously with less immunogenicity. Trials on adalimumab in UC are ongoing. A small series with preliminary data in patients with mild-to-moderate UC who had secondary failure to infliximab showed that adalimumab was well-tolerated and effective in maintaining clinical remission in a subgroup of patients with UC with lost response or intolerance to infliximab[51,52].

Parnaparin MMX

Parenteral administration of low-molecular weight heparins (LMWHs) has been taken into consideration in the treatment of UC with conflicting results. Recent experimental data proved that parnaparin sodium, a LMWH with a mean molecular mass around 5000, delivered by catheter into the colon of rat was highly effective in ameliorating dinitrobenzene (DNB)-induced colitis[53]. This lead to the suggestion that the administration of parnaparin sodium, contained in tablets delivering the product directly into the

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