Management and treatment of distal ulcerative colitis

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory condition that is confined to the colonic mucosa. Its main symptoms include diarrhea, rectal bleeding and abdominal pain. Approximately two-thirds of UC patients have disease confined distal to the splenic flexure, which can be treated effectively with topical therapy. This means the active drug can be delivered directly to the site of inflammation, limiting the systemic absorption and potential side effects. Topical treatment with aminosalicylates is the most effective approach in the treatment of these forms, provided that the formulation reaches the upper margin of the disease. Given this, the suppository formulation is the treatment of choice for proctitis and distal sigmoiditis. Thanks to their proximal spread, enemas, foams and gels represent the treatment of choice for proctosigmoiditis and for distal ulcerative colitis. Oral aminosalicylates are less effective than topical therapies in patients with active disease, while the combination of topical and oral treatment is more effective in patients refractory to topical or oral mono-therapy. Topically administered aminosalicylates play an important role in the maintenance of remission, but the long-term adhesion to therapy is poor. For this reason, the oral formulation is the first-line therapy in the maintenance of remission. Refractory patients can be treated with topical steroids or systemic steroids and TNF-alpha inhibitors in severe forms.

Introduction

The aim of treatment of ulcerative colitis (UC) is to induce and maintain both clinical and endoscopic remission. Once diagnosis has been confirmed, the main parameters to be evaluated in order to program therapy are the extension and the severity of lesions. In 90% of cases, patients with UC have a mild or moderate disease and over two-thirds of these patients have endoscopic evidence of disease confined distal to the splenic flexure.

Therefore, most of the patients with UC could be effectively treated only with topical therapy. Nevertheless, the therapeutic strategy must be decided with the patient, taking into account his or her needs or preferences. Topical treatment has the advantage of guaranteeing delivery of a high dose of principle active ingredient directly to the site of inflammation, keeping systemic absorption of the drug to a minimum and, therefore, the frequency of adverse events.

Treatment of mild-moderate active distal ulcerative colitis

Topical preparations of 5-aminosalicylic acid (5-ASA) is the treatment of choice for mild-moderate active distal UC. Different dosages and formulations have been tested in clinical studies over recent years, including suppositories, enemas, foams and gels. The various formulations differ not only in their chemical properties and dosage, but above all in their potential for proximal diffusion.1 Suppositories are the treatment of choice for proctitis and proctosigmoiditis limited to the distal colon. Scintigraphy studies have shown that the drug distributes itself mostly on the walls of the rectum and distal colon.2,3 In a multi-center randomized study of 242 patients with active proctitis, therapy with suppositories of 1 g of mesalamine was significantly more effective than hydrocortisone foam.4 Enemas, foams and gels, thanks to their retro-diffusion represent the treatment of choice for proctosigmoiditis involving the distal colon and for colitis involving the left side of the colon.

With liquid enemas, the most important characteristics for proximal diffusion are the volume administered and the viscosity of the preparation. Enemas with
bigger volumes have greater proximal diffusion, just as the foams and gels offer the advantage of prolonged retention and a more homogeneous covering of the inflamed mucosa.\textsuperscript{5-8} A randomized clinical trial comparing 5-ASA foam with 5-ASA liquid enemas showed that the foam was easier to retain and was better tolerated.\textsuperscript{9} More recently, 5-ASA gels were shown to be just as effective but was better tolerated than the formulations in enemas or foam and even easier to retain.\textsuperscript{10}

Three recent meta-analyses reviewed all clinical studies from 1958 to 1997. These clearly show that topical 5-ASA formulations are superior to placebos and to rectal corticosteroids in active distal UC.\textsuperscript{11-13} There is no evidence so far to support dose-related efficacy of topical 5-ASA therapy. Also oral aminosalicylates were shown to be effective in the treatment of active distal UC.\textsuperscript{14}

Oral therapy, although preferred by the patient is less effective than topical therapy,\textsuperscript{15} above all in forms of active ulcerous proctitis, in which mesalamine suppositories achieve significantly better and quicker results than oral administration alone.\textsuperscript{16} The lower efficacy in these patients could be explained by the relative stasis in the uninvolved segment and by an accelerated transit in the inflamed tracts that means that the inflamed mucosa has less exposure to the orally administered drug.\textsuperscript{16} Nevertheless, combined therapy with oral and topical mesalamine is more effective than the single formulation if the oral-topical combination results in a larger quantity of the drug being administered.\textsuperscript{17,18} In fact, administration of mesalamine correlates with the mucosal concentrations achieved.\textsuperscript{19} When the oral formulation alone is compared with combined oral plus topical administration, but at the same dosage, the 2 treatments have similar efficacy.\textsuperscript{20} Guidelines from the European Crohn’s and Colitis Organisation (ECCO) (statement 5B) propose topical therapy alone as first treatment choice in mild-moderate distal UC (EL1b, RG B) or combined with the oral formulation at a dose of 2 g/die (EL1a, RG A).\textsuperscript{21}

Becloamethasone dipropionate (BDP) is a glucocorticoid steroid characterized by high receptor efficacy and by an intra-hepatic first pass effect that guarantees prompt elimination impeding the inhibitory action of the hypothalamic-corticoadrenal axis.\textsuperscript{22} Treatment with topical BDP at a dose of 3 mg/die has similar efficacy to topical hydrocortisone in distal forms of UC but with a significantly reduced inhibition of the corticoadrenal action.\textsuperscript{23} More recently, topical BDP has been compared with topical mesalamine 1 g and showed similar efficacy,\textsuperscript{24} a conclusion also confirmed by meta-analysis studies.\textsuperscript{25} When administration of only a topical drug is not capable of controlling the disease, the 2 drugs can be combined, as proposed by Mulder in 1996, demonstrating the greater efficacy of the BDP-mesalamine combination than that achieved with either drug on its own.\textsuperscript{26}

In patients with active distal UC, with complete intolerance to topical therapy, one alternative is the mesalamine multimatrix (MMX) formulation. No difference in efficacy was observed in a comparison of oral MMX 3.2 g/die and topical mesalamine 4 g/die, but patients clearly preferred oral to topical treatment.\textsuperscript{27} Pharmacological treatment of mild-moderate active distal UC is summarized in Figure 1.

**Treatment of active distal ulcerous colitis refractory to traditional therapy**

Refractory colitis is a condition that most Authors define as no or partial response to traditional therapy. Management of these patients should include, above all, the exclusion of those factors that could limit or impede the efficacy of traditional therapy. Therefore, enteric infections should be excluded (\textit{Campylobacter jejuni}, salmonella, shigella, cytomegalovirus, herpes simplex virus and parasitic infections) since each one of these is associated with disease relapse. Secondly, the diagnosis should be re-evaluated, excluding through endoscopic and histological re-examination a possible cholic site of Crohn’s disease (CD).

Epidemiological studies have shown that proximal progression of the disease is observed in approximately half of the patients with proctitis or distal colitis, and this possibility must be taken into consideration in cases in which there is a worsening in the patient's clinical condition.\textsuperscript{28,29} Other factors that can cause a pseudo-refractory situation are: inadequate dosing, use of inappropriate formulations, treatment duration that is too short, intolerance to 5-ASA or reduced adherence to treatment. These should be excluded before making a diagnosis of refractory distal UC. More specifically, the correct dosage for ulcerous proctitis is represented by suppositories of 1 g. Applied once a day these induce clinical and endoscopic remission quicker than 500 mg suppositories applied twice a day and are also better tolerated by the patient.\textsuperscript{30,31}

For forms of proctitis, the formulation in suppositories has been shown to be as effective as enemas, while guaranteeing greater tolerance and adherence to treatment by the patient.\textsuperscript{32} Also, a recent prospective study clearly demonstrated that 75% of patients with active distal colitis are not treated with topical formulations.\textsuperscript{33} It should also be remembered that a suitable period of time is needed before a clinical response is seen; 6-8 weeks could be needed before clinical remission is obtained, according to the severity and the extension of the disease.

In rare cases, the use of 5-ASA formulations has led to a worsening of UC symptoms. In these cases,
One of the biggest problems in the management of UC patients is that of compliance and adherence to treatment, both with oral 5-ASA therapy and, above all, with topical formulations. Often patients use as few enemas, suppositories or tablets as possible to control symptoms. In truly refractory cases, treatment of choice is combined therapy with topical BDP or topical steroids. If the patient remains refractory, treatment with systemic steroids is indicated (methylprednisolone 40 mg/die or equivalent) or even TNF-alfa inhibitors are indicated.34

In Active Ulcerative Colitis Trials (ACT) with infliximab in moderate-severe UC, one-third of enrolled patients had distal disease involvement. On completion of eight weeks of treatment, approximately 35% of patients were in clinical remission while 65% had a reduction in symptoms and 60% had achieved mucosal cure.35 Guidelines of the ECCO (statement 5H, LE 1b, GR B) and of the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) (statement 4A, LE 1b, GR A) confirm these indications.29,36

A meta-analysis has demonstrated that topical administration of mesalamine is also the most effective maintenance treatment in distal UC. Enemas of mesalamine are superior to placebo in maintaining remission with efficacy rates of 52-92% and an odds ratio of 5.6. Rectal administration is also superior to sulfasalazin with an odds ratio of 2.3.37 A recent controlled study showed that treatment with slow release mesalamine 1 g suppositories administered 3 times a week is significantly better than placebo in preventing relapse and that in case of relapse, increasing the dose to 1 g/die is effective in inducing another remission.38 Patients who prefer not to continue topical treatment for a long period of time can also be effectively treated with oral mesalamine.39 Finally, maintenance treatment with a combination of oral and topical mesalamine was shown to be more effective in main-

**Proctitis**

5-ASA suppositories

**Proctosigmoiditis/ ulcerative colitis**

Topical 5-ASA or BDP (enemas, foams, gel)

Oral 5-ASA-MMX

Combination oral 5-ASA + topical 5-ASA/BDP

Figure 1. Traditional therapy for mild-moderate active distal ulcerative colitis.

Figure 2 shows the management flow chart of distal UC refractory to traditional therapy.

**Maintenance therapy of distal ulcerative colitis**

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Figure 2. Management of mild-moderate active distal ulcerative colitis refractory to traditional therapy.

1. Verify the extent of refractoriness
   - Exclude enteric infections (*Campylobacter jejuni*, salmonella, shigella, cytomegalovirus, herpes simplex virus and parasitic infections)
   - Exclude disease progression/cholic localization (endoscopy + histological)
   - Evaluate adequacy of dosage (1 g vs 500 mg suppositories)
   - Evaluate adequacy of formulation (suppositories – proctitis, enemas – high forms)
   - Evaluate duration of treatment (at least 6-8 weeks needed)
   - Exclude intolerance/allergic reactions to the drug
   - Evaluate adherence to treatment

2. Modify therapy
   - Combine topical 5-ASA with systemic 5-ASA
     - Response
     - Non-response
       - Topical BDP/topical steroid
         - Response
         - Non-response
           - Systemic steroids or biological therapy with anti-TNFα
Maintenance of remission and could be useful in patients at high risk of relapse.40-42

Oral mesalamine is also indicated in patients who have obtained clinical remission with systemic steroids but not in patients with corticoadependence in whom the treatment of choice for maintaining remission is azathioprine. Also infliximab is effective in maintaining remission even though clinical studies were carried out for only one year. The experience of single centers for longer periods of time has shown good drug efficacy and safety.

Maintenance therapies for distal UC are summarized in Figure 3.

**Conclusions**

In conclusion, topical treatment with aminosalicylates is the treatment of choice for patients with active mild or moderate distal UC. The choice of formulation and dosage must be based on an evaluation of the extension and the severity of the inflammatory lesions. Also oral aminosalicylates are effective in active distal UC but to a lesser degree than topical formulations. Therapy with topical mesalamine is the most effective treatment for maintaining remission in distal UC, but those patients who prefer not to continue treatment with topical formulations for long periods of time can be effectively treated with oral mesalamine. The combination of oral and topical mesalamine is indicated for inducing remission in refractory patients and in maintaining remission in patients at high risk of relapse. The choice of therapy for maintaining remission depends on how the patient achieved control of the disease. Treatment with oral or topical mesalamine, in selected cases, is the treatment of choice when the acute phase was treated with mesalamine. Azathioprine can be used when the acute phase was treated with systemic steroids, or infliximab when remission was achieved with infliximab.

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**Figure 3. Maintenance therapy for distal ulcerative colitis.**

- **Non-steroid-dependent patients**
  - Topical 5-ASA (enemas, gels, suppositories)
  - Oral 5-ASA/5-ASA-MMX (non-compliant patients)
- **Steroid-dependent patients**
  - Azathioprine/β-mercaptopurine
  - Anti-TNFα
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