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Ulcerative Proctitis

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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of digestive tract of unknown cause. This disease is characterized by a chronic course with alternating periods of activity and clinical remission. The incidence of UC in America has a range extending from 2.2 to 14.3 per 100,000 population per year [1]. The continuous involvement from the rectum to proximal presents an extension that is variable among patients and in the course of the disease [2]. The extension of the compromise determines its clinical presentation, the treatment and prognosis of UC [2]. Depending on the size, it is classified as proctitis or ulcerative proctitis (UP) when it affects the rectum; left or distal colitis when inflammation is distal to the splenic flexure and extended colitis when the inflammation reaches the transverse colon, right or has an involvement the entire colon [2]. Several studies have attempted to establish the factors that determine the extension of the involvement. Among the factors associated with rectal compromise are middle age patients, absence of serious bleeding and absence of extraintestinal manifestations [3]. However, these factors have not been replicated, so even today there are no factors strongly related to PU [1,4]. The mayority of the new cases are diagnosed in adults as a PU or distal colitis [1,5]. Although initial reports indicated that PU had a low frequency [6], recent studies reported that incidence has been increasing up to 48% and 60% [4,7], whereas the incidence of colitis has been decreasing in most geographic areas [8]. Some authors have suggested that PU represents a completely different clinical entity from the CU [8-9]. However, most authors agree that the PU is an initial form of CU with the potential to extend into the proximal segments of the colon [10-12]. Ulcerative proctitis, unlike other forms of more extensive presentation of CU, is clinically characterized by bleeding and or rectal pushing, without systemic symptoms or abnormal physical examination or laboratory tests and can be treated solely with topical rectal therapies [7].

The 5-aminosalicylates (5-ASA) and corticosteroids are available for topical use as a local anti-inflammatory agents [7]. These drugs can get straight to the site of inflammation, which decreases systemic absorption and minimize potential side effects [7,13]. The oral 5-ASA is also an alternative prior to the use of corticosteroids, as these have a number of risks and limitations in short and long term use, reserving for very severe active PU [14]. When refractory to previous treatment, drugs that can be used to induce and maintain remission are immunomodulators such as azathioprine [15], 6-mercaptopurine [16] and/or Infliximab therapy [17-18].

Mortality and cancer risk associated is no greater than the general population [2], as the PU is usually considered a mild form of UC. However, about 23% of PU patients can reach a colectomy [19] and from 41 to 54% of patients will increase proximally its compromise after 10 years of disease [2-11], indicating that the PU is not always a mild disease.

2. 5-ASA preparations

Topical treatment have been used for a long time and have offered the advantage of delivering a high dose of the compound directly to the site of inflammation, minimizing absorption and therefore limiting the frequency of systemic adverse events [20]. Rectal preparations of 5-ASA are the treatment of choice for distal UC and mild to moderate PU. Various forms of this compound have been tested in different trials, including suppositories, enemas, foams and gels. Mesalazine suppositories 1 g per day administered dose, preferably at night, should be considered as the treatment of choice for active PU, being superior to oral 5-ASA with 91% versus 41% as a induction of the remission [5,11,21,22,23,24]. Scintigraphic studies have shown that this drug consistently reaches the rectum and distal sigmoid to a length of 18-20 cms. from the anal verge [25], being as effective as enemas, but better tolerated and preferred by patients [26]. The dosage of 5-ASA enemas is 4 g in 60 ml with a dosage of 1-2 times daily for 4 weeks. Although equally effective as the enema, foams and gel might offer the advantage of longer intraluminal retention, more homogeneous distribution in the inflamed mucosa and better tolerance by the patients [26,28]. Maintenance treatment is indicated for all cases and the minimum is a one-year treatment [29-30]. A small percentage of patients who could completely stop the therapy, because the relapse is up to 86% to the completion of a twelve months treatment [31]. The algorithm of management of active PU and remission is shown on Fig.1.

3. 5-ASA oral administration

When the patient refuses the use of topical agents or if after 2-4 weeks of treatment with 5-ASA rectally there is no response, the oral 5-ASA (mesalazine or sulfasalazine) should be considered as an alternative. Randomized clinical trials have shown benefits of adding oral 5-ASA compounds (mesalazine) with a dose greater than 3 g per day in active distal UC [32]. No studies demonstrate the efficacy of these compounds as oral monotherapy for PU, although had been proven effective for more extensive UC. It has been postulated that it would be especially useful to prevent proximal extension of disease in the maintenance phase of treatment [32-33]. The administration might be associated with allergic phenomenon and headache among other side effects [13].

4. Steroids in the treatment of PU

For those patients in whom there is no response after 2-4 weeks of topical treatment with aminosalicylates is considering the use of corticosteroids. Several steroids have been effectively administered rectally (suppositories, enemas, foams), including hydrocortisone (100 to 200 mg in 60 to 200 ml), betamethasone, prednisolone phosphate [34] and recently the budesonide, included as a therapeutic agent [35]. Hydrocortisone enemas were significantly superior to placebo with 55% versus 10% induction of remission [36] and have comparable efficacy to systemic corticosteroids and less inhibition of the hypothalamic-

pituitary-adrenal axis, as there is direct absorption through the superior and middle rectal veins into the systemic circulation, without passing through the hepatic portal system [35]. Budesonide has been extensively studied during the last decade, when compared with mesalazine and other corticoids. One study compared the response of budesonide foam and hydrocortisone foam in patients who failed to mesalazine, achieving a 52% response in the budesonide group and 37% remission in the group using hydrocortisone foam [36]. Remission with budesonide foam was achieved by 19% of the patients with a minimum dosage of 2 mg per 100 ml for a period of at least 6 weeks, but doses of 8 mg in 100 ml achieved remission in a higher percentage of 27% 4% versus placebo [35-37]. No studies support the use of steroids for maintenance of remission of PU [1]. Despite the benefits delivered by 5-ASA compounds and steroids for rectal administration, some patients fail to achieve remission and require additional therapy. The failure of the administration of drugs is considered the most important factor of refractoriness of the PU, so that by reintroducing the therapy, it could achieve a good response. Patients should also be evaluated for hypersensitivity to aminosalicylates, characterized by an allergic colitis, abdominal pain and diarrhea [1] and by examination or endoscopy to rule out a secondary infection by Clostridium difficile or cytomegalovirus, an extension of the disease to proximal segments the colon or the presence of Crohn's disease. Infection should also be excluded in refractory patients. Patients not responding to therapy, rectal and/or oral (5-ASA and steroids) are in a serious problem, and the options include azathioprine (AZA), 6-mercaptopurine (6-MP), immunomodulators, infliximab, antibiotics and even surgery [1].

5. Antibiotics

Unlike Crohn Disease (CD), the effectiveness of antibiotics in ulcerative colitis has not been proven [1]. Both ciprofloxacin, tobramycin and metronidazole have been studied, despite a clear trend toward improvement, showed no superiority in terms of the induction or maintenance of remission in UC [38]. Although in some studies there was a clinical/endoscopic response about 80%, sustained remission was not obtained, and recurrence was similar to placebo [39]. There are no studies showing the effect of the antibiotics in PU.

6. Azathioprine and 6-mercaptopurine in PU

The AZA and 6-MP are a key part in the therapy of IBD [40], mainly in steroid-dependent and resistant cases. Strong scientific evidence available on the role of AZA and 6-MP in UC is more limited than in CD [41], has been released placebo-controlled studies evaluating the efficacy of these drugs in the induction of remission in patients with active UC, in which it is established that AZA had no effect in achieving remission, but decreases the proportion of relapse [42-43]. Nor has largely been assessed for the maintenance of remission of UC. There are no studies evaluating exclusively the effectiveness of these compounds in PU or distal colitis, but it is considered as a valid alternative in the treatment [32].

7. Cyclosporine

Several studies show that cyclosporine is effective in inducing remission in severe UC [44]. The relatively fast response makes the use of cyclosporine potentially attractive, but long-

term benefit are unclear, especially when life-threatening side effects can occur such as nephrotoxicity and opportunistic infections. There are no randomized trials showing the effectiveness of immunosuppression for refractory PU and studies are only anecdotal [45-46].

8. PU and biological therapy

Biologic therapies attempt to restore the balance between pro-inflammatory and anti-inflammatory effects observed in IBD. Infliximab is a chimeric monoclonal antibody (IgG) derived from recombinant DNA, consisting of genes of human and murine origin. These bonds and neutralizes tumoral necrosis factor alpha (TNFα), thus interrupting the sequential cascade of activation of inflammatory pathways mediated by this cytokine. Infliximab was reviewed in controlled randomized studies ACT 1 and ACT 2, demonstrating its benefit in patients with moderately to severely active UC, as well as refractory UC [47]. However, these tests excluded patients with only PU. Among the advantages of this drug include a rapid onset of action and the possibility of achieving endoscopic and histological normalization of the mucosa. It showed a 30% remission and 60% improvement in patients and close to 70% of the patients refractory to 5-ASA, corticosteroids or AZA/6-MP respond to Infliximab [48]. However, the use of infliximab in this condition is poor [1]. The algorithm for management of refractory PU is shown on Fig.2.

9. Other investigational therapies

Transdermal patches and nicotine enemas [47], low molecular weight heparins [50], light chain fatty acids rectal administration [45] and probiotics [51] have been dismissed for handling the left CU or PU, given the low level of evidence and its low efficacy in inducing remission in active crisis.

10. Surgery in ulcerative proctitis

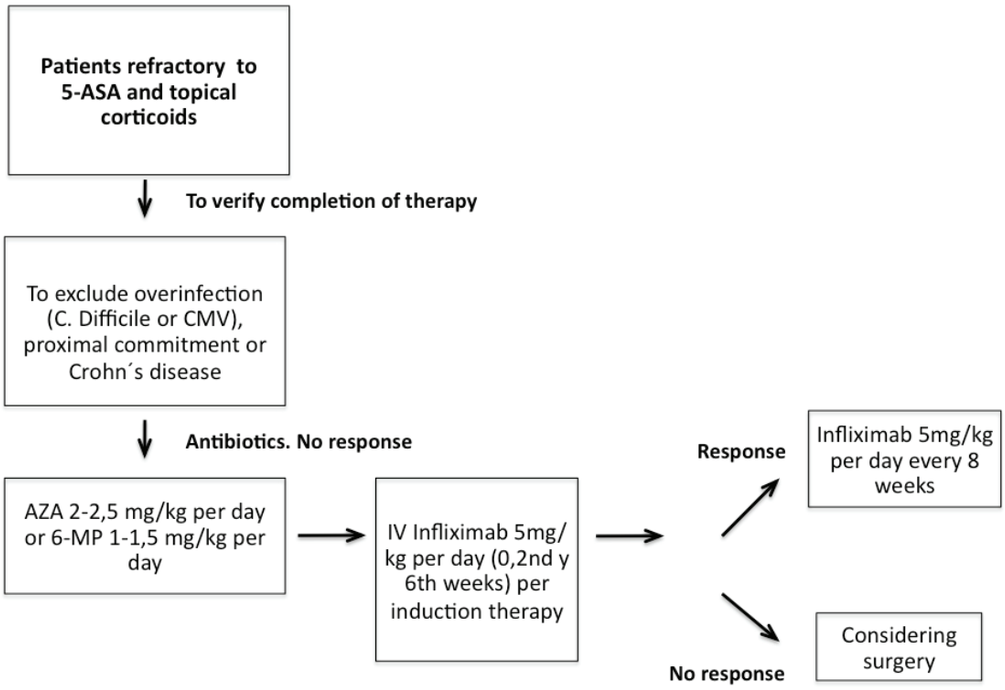
Although PU can be sometimes refractory to all therapies available, it is rare surgery being considered as a treatment option. Surgery has being used between 2-9% at 5 years [52-53] to 23% at 20 years [54]. For those patients who do require surgery, proctocolectomy with end ileostomy or the confection of an ileal reservoir-anal anastomosis are the options [1]. We emphasize that no published studies that demonstrate short or long term results of surgery in refractory PU.

11. What is the future treatment for the PU?

Protocols of therapeutic strategies based on the best scientific evidence has improved significantly the prognosis of patients with PU in recent years. The availability of biological therapies and the advances in colorectal surgery opens up new prospects for evaluating the usefulness of these alternatives in the refractory PU to conventional treatment. This has been associated with the development of new drugs which would yield an improvement in symptoms with fewer side effects, which are not yet available.

The use of epidermal growth factor (EGF) enemas has delivered good results and it is an effective treatment for ulcerative left colitis and mild to moderate PU associated with oral mesalamine [55]. This compound stimulates the migration, proliferation and repair the

injuries of the gastric, intestinal and colonic mucosa. Studies shows a 83% of remission in the EGF-enema group vs 8% of placebo group after 2 weeks of treatment. Despite reducing the activity and inducing clinical remission, clinical studies should be conducted to compare EGF versus high doses of mesalamine or corticosteroids [55]. Rebamipide is an aminoacid 2(1H)-quinolinone derivate, used for the protection of gastric and duodenal mucosa. It acts through the suppression of neutrophil functions, stimulation of epithelial cell regeneration and increased the expression of epidermal growth factor (EGF) and its receptor. Through a prospective study was found that Rebamipide enema in distal colitis and active PU local topical therapy could be effective in the treatment of mild to moderate active disease [56]. There were no adverse effects related to the Rebamipide in the 16 patients included in the study [57]. Tacrolimus is an immunosuppressive drug produced that has been used mainly in transplantation and autoimmune diseases. The mechanism is similar to cyclosporine, but is better tolerated and is a hundred times more potent than this. Acts directly on T-lymphocytes, inhibiting the transcription of IL-2, decreasing lymphocytic response to antigens [58] and inhibiting the release of inflammatory mediators from mast cells and basophils. Lawrence et al [58] achieved complete remission after 8 weeks of treatment with rectal tacrolimus in 75% of the patients studied, all resistant to conventional therapy. The patients who did not responded, presented proximal proggresion of the disease, where the compound did not reach topically. Randomized clinical trials are needed to evaluate its effectiveness versus placebo.



*Adapted from Clinical Guidelines. Inflamm Bowel Dis. 2006;12:972-978 Regueiro et al.

Fig. 1. Algorithm of management of active PU

In summary, topical administration of 5-ASA suppositories, enema or foam is the preferred treatment for most patients with PU. The local administration of 5-ASA is more effective than oral 5-ASA, but the combination of oral and topical should be considered for those without an adequate response to any of these therapies separately. Topical corticosteroids are the second-line treatment either as monotherapy or in combination with topical 5-ASA. Maintenance treatment is indicated in all cases and corresponds to the preferential use of topical 5-ASA, with the oral formulation is also an alternative. Refractory patients or intolerant to 5-ASA may require immunomodulators or biological therapy. Systemic steroids or surgery should be used in very special cases.

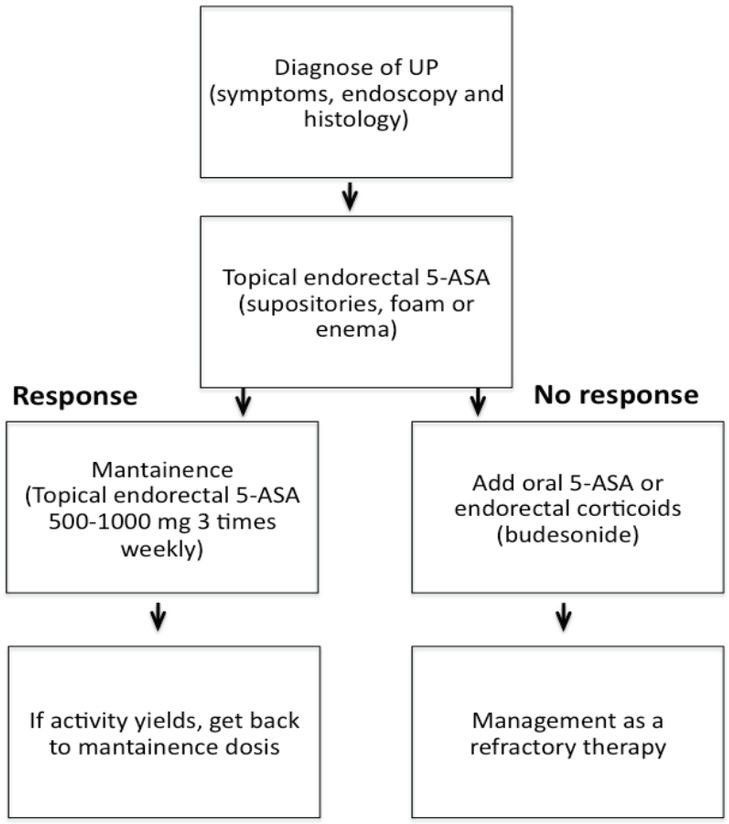


Fig. 2. Algorithm for management of refractory PU

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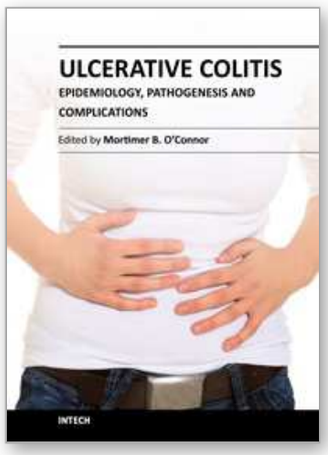

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