The role of aminosalicylates in the treatment of ulcerative colitis

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Abstract

Aminosalicylates (5-ASA, sulfasalazine and mesalazine) play a central role in the treatment of ulcerative colitis (UC). For acute treatment of mild to moderate flares and in maintenance treatment, their efficacy has been established. Since ulcerative colitis is limited to the distal colon in two thirds of the patients, topical therapy also plays an important role. In mild/moderate active disease 5-ASA 4 g/d is as effective as oral corticosteroids. Ulcerative proctitis is treated with 2 x 500 mg or 1 x 1 g suppositories and proctosigmoiditis with 1 to 4 g enemas. Oral 5-ASA is also safe in maintenance treatment and is generally well tolerated.

The risk of colorectal tumours is increased in patients with long-standing ulcerative colitis and epidemiological evidence indicates that chronic 5-ASA treatment reduces this risk. However, at present there is insufficient evidence to maintain patients on life-long 5-ASA maintenance treatment for this indication. (Acta gastroenterol. belg., **2002**, 65, **196-199**).

Key words : ulcerative colitis, aminosalicylates, safety, sulfasalazine, mesalazine.

Introduction

Ulcerative colitis and Crohn's disease are the two main chronic inflammatory bowel diseases in the Western world. Contrary to Crohn's disease, ulcerative colitis is always limited to the mucosa and submucosa of the colon and it extends continuously from the anus proximally in the colon. In two thirds of the patients, the disease is limited to the left colon. Ulcerative colitis is characterised by flares and periods of limited disease activity or remission and this requires both potent induction therapy and safe maintenance medication. The incidence of ulcerative colitis peaks in young adults. Consequently, the drug's safety in the context of fertility and pregnancy is essential for a large number of patients.

Aminosalicylates are a category of medicines containing the active molecule 5-aminosalicylic acid (5-ASA). Sulfasalazine consists of an antibiotic sulfapyridine group and the anti-inflammatory agent mesalazine (5-ASA) in an azo-bond (called mesalamine in the USA). 5-ASA has been used for many years in the acute and maintenance treatment of ulcerative colitis, but this article will deal with the permanent role of these products in the current management of the disease.

Treatment of acute ulcerative colitis

Treatment of an active colitis should be adjusted according to the severity of the disease activity, the patient's personal history and the risk of complications. Usually, a distinction is made between mild, moderate and severe activity (see table 1). The treatment of choice for mild disease (3-5 stools/day, limited presence of blood and abdominal pain during defaecation in particular) consists of oral 5-ASA at a dose of 4-6 g/day, in combination with topical preparations for rapid symptom relief if necessary (table 2) (1, 2, 3).

Table 1. — Classification of ulcerative colitis disease activity

mild disease	3-5 stools per day/ urgency blood on stools mild cramps during defaecation little impact on quality of life
moderate disease	4-6 bloody stools per day moderately severe abdominal pain mainly during defaecation fatigue some impact on general condition
severe disease	> 6 bloody stools per day fever > 37.5(C, tachycardia anaemia and RBC sedimentation > 30 mm/h RX/ colon dilation and 'thumbprinting'

Mesalazine or 5-ASA has no antibiotic sulfapyridine group and is tolerated by a larger group of patients. Indeed, 80% of the patients with an intolerance of sulfasalazine tolerate mesalazine (5-ASA) without side effects. All oral formulations of 5-ASA are protected from gastric degeneration.

Since the inflammatory reaction is located in the colon in ulcerative colitis, diarrhoea will generally not affect the release. Eudragit-coated preparations (Claversal, Colitofalk, Asacol) and Pentasa (continuously releasing microgranules) are available on the Belgian market. The release from the Eudragit-associated formulations depends on the luminal pH, though it is generally accepted that the differences between commercial preparations are only of limited clinical relevance. Since extensive clinical studies have revealed only minimal differences in efficacy between a daily dose of 2 and 4 g (1), it is highly unlikely that small differences in bioavailability between existing preparations will have an impact on the efficacy.

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Table 2. — Treatment of acute ulcerative colitis

disease activity	proctitis	left-sided	pancolitis
mild	topical 5-ASA/GCS	topical 5-ASA/GCS + oral 5-ASA	oral 5-ASA
moderate	topical 5-ASA/GCS	oral GCS	oral GCS
severe	increase dose	IV GCS + cyclosporine	
refractory	topical 5-ASA + GCS oral steroids alternatives	restorative proctocolectomy	

note : GCS = glucocorticosteroids, e.g. methylprednisolone 0.5-1 mg/kg starting dose.

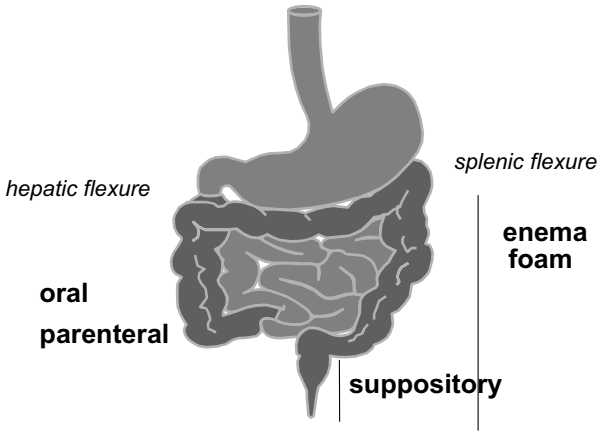

Fig. 1. — Schematic representation of the theoretical range of topical 5-ASA preparations. In patients with colitis extending further than the splenic flexure systemic treatment is always required.

Complications with acute 5-ASA treatment are very rare and will be discussed further under maintenance treatment. Moderate flares (4-6 bloody stools/day, abdominal pain and a certain impact on daily functioning) are usually treated with oral steroids (e.g. methylprednisolone 0.5-1 mg/kg). Steroid treatment is gradually phased out after symptom remission (usually 5-10 days). Topical 5-ASA and topical steroids (budesonide, hydrocortisone, betamethasone, beclomethasone dipropionate), or a combination of both can be added for rapid symptom control. Severe flares (> 6 bloody stools, fever, tachycardia and biochemical markers of inflammation) generally require hospitalisation for intravenous therapy and monitoring. In this case, intravenous steroids and cyclosporine are the products of choice. However, in the event of insufficient response after 5-7 days, colectomy should always be considered (table 2) (4).

Topical treatment with aminosalicylic acid

In distal and leftsided UC topical treatment certainly has a place in the management. The great advantage is high local concentrations.

It is generally established that proctitis can be effectively treated with suppositories, whereas the sigmoid can be reached with foam preparations and the descending colon with enemas (Fig. 1) (5). Active disease does not influence the reach of topical treatments, but may affect the retention of the enema. Treatment is initiated with a high daily dose (1 to 4 g enema, 1 g suppository) of topical 5-ASA until satisfactory control of symptoms is achieved (usually 5-21 days). The intervals between administrations can subsequently be increased progressively (6,9,11). It has been shown that 1 g enemas are as effective as the higher doses (7). A suppository of 1 g once daily is as effective as 2 suppositories of 500 mg and probably has a favourable effect on patient compliance. Studies have shown that topical 5-ASA (enemas) are more efficacious in the treatment of left-sided ulcerative colitis than topical steroids (8). The advantage of 5-ASA compared to placebo was reflected in both symptom control and in endoscopic and histological improvement. There is considerable absorption of topical steroids, particularly during active disease, thus significantly more side effects can be anticipated with this treatment. Recently, however, products such as budesonide (entocort(-enema) and beclomethasone-dipropionate (generic formulation), alone or in combination with 5-ASA, are used increasingly since they produce fewer systemic side effects due to an extensive first-pass metabolism in the liver. Steroids are not indicated in maintenance treatment. Topical 5-ASA in combination with oral administration should certainly be considered (see below). This combination offers two advantages. First there is the clinical impression that in patients with colitis extending beyond 35 cm, enemas alone are less effective. Secondly, in 30-40% of the patients with proctosigmoiditis, the disease extends to the proximal colon. Other topical treatments such as nicotine, local anaesthetics, butyrate and tacrolimus are in an experimental stage, though encouraging results have been obtained with some of them.

Maintenance treatment of ulcerative colitis

Colectomy is considered a curative treatment for ulcerative colitis, but the procedure is reserved for very

severe diseases (toxic megacolon), refractory disease or dysplasia in the colonic mucosa. In addition, a third of the patients with a ileo-anal J-pouch reconstruction after colectomy will develop acute pouchitis, which will become chronic in about 8%. For these reasons it is important for the clinician to dispose of a safe long-term treatment for ulcerative colitis. Since ulcerative colitis is characterised by flares and episodes of remission, maintenance treatment is aimed at maximal prolongation of the intervals between flares and at limiting the severity of the flares. In clinical trials, the efficacy of maintenance treatment in IBD is generally based on the percentage of patients presenting a relapse within the studied follow-up period. In these studies, 5-ASA is consistently superior to placebo and equivalent to sulfasalazine (1). However, the optimal maintenance dose of 5-ASA is an element of discussion. Contrary to acute treatment, where it makes sense to use high doses up to and over 4 g, no additional benefit related to doses over 1.5 g has ever been established in oral maintenance treatment. In practice, a daily dose of 2 to 3 g is generally maintained (1,10). However, some patients require a higher dose, so it is probably advisable to adjust the maintenance dose of 5-ASA to suit each patient's requirements. There is also sufficient experimental evidence to support topical maintenance therapy in distal colitis (10). If long-term topical treatment is acceptable to the patient, this should certainly be considered. When more aggressive immunomodulating maintenance therapy with azathioprine or 6-mercaptopurine (in corticosteroid-dependent patients) is decided in patients, the 5-ASA treatment is generally not interrupted. At present, however, no controlled studies are available on the added benefit of this combination versus azathioprine in monotherapy.

Maintenance treatment with 5-ASA is very well tolerated contrary to long-term treatment with sulfasalazine, which causes side effects in 10-40% of the patients. 80% of patients with intolerance of sulfasalazine experience no side effects with chronic 5-ASA treatment. The antibiotic sulfapyridine group is probably responsible for most side effects with sulfasalazine. The side effects of long-term use of 5-ASA are very limited to rare cases of pancreatitis and bone marrow depression in addition to diarrhoea and elevated transaminase levels. The renal toxicity of 5-ASA is controversial since the rare cases of interstitial nephritis cannot be attributed to the treatment with certainty. A French study based on official reports mentions an incidence of 9 cases of severe side effects per million days of treatment (12).

There is no consensus about how long after the last flare maintenance treatment should be continued. In this context, an Italian study revealed that in a subgroup of patients, who had been in remission for 2 years, maintenance treatment could be discontinued without an early relapse of colitis (13). This subgroup appeared to be older patients with a longer interval since the onset of the disease.

Patients with longstanding ulcerative colitis have a higher risk of colorectal carcinoma. A higher risk of carcinoma is found only in the segments with long-term inflammation and the pathogenesis probably differs from that in sporadic colonic tumours. At present, there is indirect evidence that long-term treatment with 5-ASA can have a protective effect against the development of colonic carcinoma, though more studies are required before 5-ASA chemoprophylaxis is introduced as a general guideline (14). Patients with a family history of colonic tumours or polyps have an even greater risk of colonic carcinoma and this group should certainly be followed endoscopically on a regular basis.

Conclusion

Oral and topical aminosalicylates have an established role in the treatment of mildly to moderately active ulcerative colitis. They are also used as maintenance treatment and for refractory patients azathioprine/6-mercaptopurine is the only alternative at the moment. Though the initial dose of 5-ASA is 3-4 g orally and 1-4 g topically, 2 g appears to be sufficient as maintenance dose. Nevertheless, it is often necessary to adjust the dose individually. Long-term treatment with 5-ASA is safe and well tolerated. The role of these products in chemoprevention of colorectal tumours in patients with colitis is an interesting topic for further research.

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