THE MANAGEMENT OF REFRACTORY DISTAL COLITIS

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INTRODUCTION

Distal ulcerative colitis that is refractory to conventional treatment is commonplace, but the optimum management remains unclear. Indeed, the very definition of refractoriness is itself controversial. Nevertheless, it is essential to establish a strategy for such patients, otherwise an idiosyncratic series of therapeutic trials will ensue during which both the patient and doctor become demoralised by persistent symptoms.

By definition, refractoriness implies an inadequate response to treatment, for which both response and treatment need to be specified. An adequate response must mean a return to normal bowel function which, for the sake of an objective criterion, means three or fewer stools each day without visible bleeding or urgency. All too frequently patients have to put up with inadequately treated disease because 'clinical improvement' is considered by their doctors to be an acceptable response. This affects clinical trials as well as clinical practice, making therapeutic comparisons difficult.[1] In therapeutic trials, the three criteria that should be used to evaluate response are clinical, endoscopic and histological remission. Of these, the key criterion is clinical remission, since this is what matters to the patient.

What constitutes conventional treatment is more debatable. For some, this means treatment with oral aminosalicylates and topical steroids, with refractoriness defined as an inadequate response after six to eight weeks.[2] Others use systemic steroids and define refractoriness as persistent symptoms due to colonic inflammation confined to the rectum or rectosigmoid area despite treatment with oral and topical steroids for six to eight weeks. Using this latter definition, the prevalence of refractoriness is around 20%. In the one small study to examine this prospectively in clinical practice, eight patients out of 40 with active distal colitis had a refractory episode. Of these, three responded to further oral steroids and mesalazine enemas, one to treatment of proximal constipation and three to intensive intravenous treatment. One patient came to colectomy.[3] Numbers are small, but are the first to represent clinical practice outside a randomised controlled trial.

WHY DOES DISTAL COLITIS BECOME REFRACTORY?

The reasons that distal colitis becomes refractory include poor patient compliance with therapy, inadequate concentrations of the active drug, the wrong drug or co-existent infection. Poor rectal compliance and physiological factors such as depleted cellular steroid receptor expression may also contribute to refractory symptoms and it is worth considering briefly these issues.

Surprisingly, few data exist on drug compliance in colitis, in spite of well-documented poor compliance in other chronic conditions. In a rare study to report compliance, 14% of patients with active colitis omitted >20% of prescribed doses, although this must be an underestimate since it was derived from the 43–63% who actually returned unused medication for counting.[4] As long as the patient is taking the medication, inadequate drug concentrations will reflect the delivery system. The pharmacokinetics of *rectal* therapy are, however, usually neglected. A suppository only coats the rectum as far as the rectosigmoid junction and, once dissolved, has greater viscosity and mucosal adherence than liquid or foam enemas. Enemas travel further but relatively little medication is left behind and retained in the rectum. In 31 patients with active colitis, less than ten per cent of 30 ml, 60 ml or 100 ml enemas remained in the rectum as assessed by scintigraphy, with most (66–99%) being deposited in the sigmoid colon.[5] Suppositories are better tolerated, achieve a higher concentration of drug where it matters in the rectum and may be effective where enemas have failed. Apart from the delivery system, the choice of drug is clearly relevant. Topical corticosteroids, for instance, are less effective than topical mesalazine.[6] It is also possible that concurrent medication, such as non-steroidal anti-inflammatory drugs, or infection might be the cause of refractory colitis.

The prospect of being able to predict refractoriness to steroid treatment by techniques such as evaluating steroid receptor expression is intriguing. Steroid receptors express either an active α chain or a β chain that is an intracellular antagonist of glucocorticoid activity. β chain mRNA was detectable in ten out of 12 poor responders to corticosteroids, but in only one out of 11 responders and two out of 20 healthy subjects.[7] The sensitivity of T-cell receptors to steroids has also been examined, using the concentration of dexamethasone necessary to inhibit proliferation when stimulated by phytohaemaglutinin. In severe colitis treated with intravenous steroids, all 11 complete responders had T-cells sensitive to <150 nM dexamethasone, compared to two out of seven poor responders.[8] Persistent symptoms can also be due to poor rectal compliance as a consequence of chronic inflammation, even in the absence of active inflammation. This causes urgency and stool frequency by triggering the desire to defecate at low stool volumes.

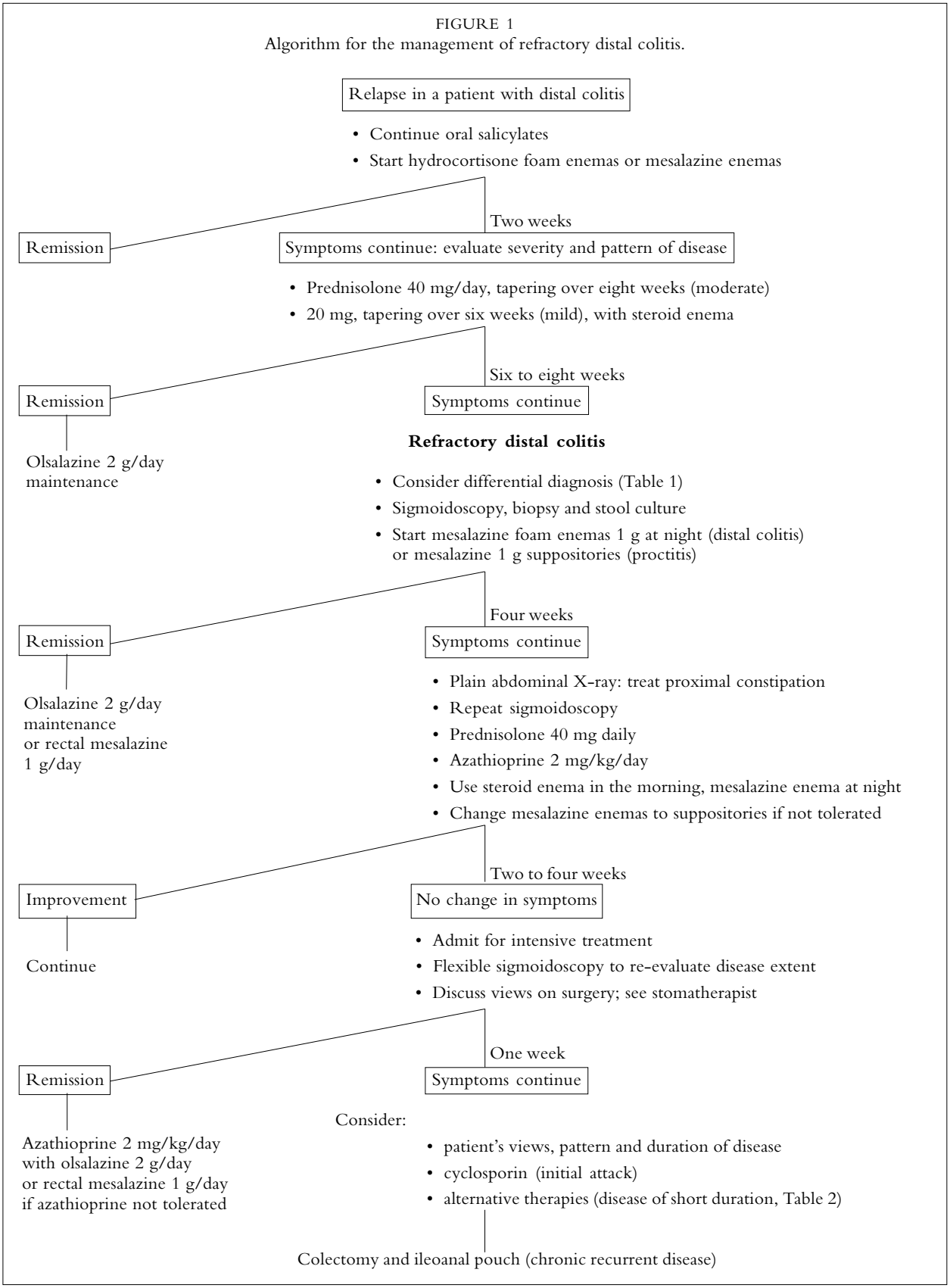
MANAGEMENT OF ACTIVE DISEASE

The importance of a strategy to avoid a random sequence of therapeutic trials in refractory distal colitis cannot be over-emphasised. The stages should be discussed with the patient, who usually appreciates the sense of direction, even if the response remains poor. A personal approach is illustrated in Figure 1. Much, however, depends on the initial approach to treatment.

Standard treatment of active distal colitis

Active distal colitis is commonly first treated with rectal corticosteroids and high doses of oral aminosalicylates.

FIGURE 1
Algorithm for the management of refractory distal colitis.



Controlled trials, however, show that this fails to achieve remission in at least half the mild to moderate attacks of colitis within six weeks. For example, in 158 patients given Asacol 2·4 g, 1·6 g, or placebo daily with rectal steroids, the remission rate after six weeks was 49%, 43% and 23% respectively.[9] In a meta-analysis of treatment with rectal steroids for up to eight weeks, pooled remission rates by symptomatic, endoscopic and histological criteria were 45%, 34% and 29% respectively.[6] In the most recent meta-analysis of oral aminosalicylates for active disease involving

19 trials and 2,032 patients,[10] although mesalazine was more than twice as effective as placebo (OR 0·39; CI 0·29–0·52), it was no better than sulphasalazine (OR 0·87; CI 0·63–1·20). Further, higher doses of aminosalicylates were not shown to be any more effective than standard doses for treating active ulcerative colitis. Unfortunately, meta-analyses have not addressed the speed of response. Since it is often the speed of response that matters to patients, who want rapid resolution of symptoms that are interfering with their life, this type of approach should only be tried for a limited period before switching to more effective therapy.

The modest response to oral aminosalicylates contrasts with two early studies on oral and rectal corticosteroids. Oral prednisolone (starting at 40 mg daily) with steroid enemas induced remission in 77% of 118 patients with mild to moderate disease within a fortnight, compared to 48% treated with 8 g/day sulphasalazine and steroid enemas.[11] Similar findings were reported by Lennard-Jones[12] who found the combination of oral and rectal steroids to be better than either alone. An appropriate regimen for moderately active disease (bloody stool frequency five to six times daily with no systemic features) is prednisolone 40 mg/day for one week, 30 mg/day for one week, then 20 mg/day for one month before decreasing by 5 mg/day/week. Topical steroids can be given twice daily whilst there is visible bleeding, then once at night until oral steroids cease. Treatment for mild relapses (bloody stool frequency ≤four times daily) can start at prednisolone 20 mg/day, also with topical steroids. Shorter courses are associated with early relapse and doses of prednisolone ≤15 mg day are ineffective for active disease.[13]

Initial approach to refractory distal colitis

If symptoms persist after oral and topical steroids, distal colitis can appropriately be called refractory and the diagnosis needs to be reviewed (Table 1). Assuming none of these conditions apply and inflammation remains active, then further treatment is appropriate, starting with a change in topical therapy. The properties and distribution of topical preparations (suppository, foam, liquid enema or gel) need to be taken into account to ensure the maximum concentration of 5-aminosalicylic acid (5-ASA) at the site of disease activity.

Changing topical therapy: Topical mesalazine is clearly more effective than topical steroid. In a meta-analysis of seven trials, rectal mesalazine was superior to topical steroids at inducing symptomatic (OR 2·42; CI 1·72–3·41), endoscopic (OR 1·89; CI 1·29–2·76) or histological remission (OR 2·03; CI 1·28–3·20).[14] In the largest trial of 295 patients treated for four weeks, 52% on Asacol foam enemas entered remission compared to 31% on Predfoam ($p < 0·001$, intention to treat analysis).[15] Higher doses of topical mesalazine, however, do not provide additional benefit. For example, in a study of 113 patients with active distal colitis, remission rates after 30 days on 1 g, 2 g and 4 g enemas were 63%, 67% and 72% respectively.[16] There may also be some advantage in combining topical steroids with 5-ASA enemas. Significantly better clinical, endoscopic and histological improvement occurred with both beclomethasone dipropionate (3 mg) with mesalazine (2 g) enemas than with either agent alone.[17] Consequently, a combination of corticosteroid enemas in the morning and mesalazine enemas in the evening is a useful practical approach for refractory distal disease.

Given that topical salicylates are more effective than topical steroids, it might well be asked why these are not always used initially. This would be entirely reasonable, but in the UK health care system cost is a limiting factor. At current prices, an eight week course of prednisolone starting at 40 mg/day costs <£2, whereas steroid foam enemas cost around £28 and salicylate enemas cost £160 or more for eight weeks. This may not necessarily be the case in other countries. Many gastroenterologists use mesalazine enemas before oral corticosteroids, although direct comparative data on relative efficacy and tolerability are lacking.

The neglected role of suppositories: Since <10% of a mesalazine enema can be detected in the rectum after administration,[5] suppositories are often more appropriate than enemas and can be used as an adjunct to treatment. The type of suppository rather than the dose appears to matter. In a study of 50 patients with active proctitis, a single high dose suppository (Pentasa 1 g) was more rapidly effective than 500 mg (Claversal) suppositories twice daily.[18] Clinical (and endoscopic) remission occurred in 64% (52%) within two weeks on Pentasa, compared to 28% (24%) on Claversal suppositories ($p < 0·01$), although there was no difference after four weeks of treatment. Not surprisingly, once daily therapy is more popular with patients and compliance appears to be better with suppositories than with enemas.[4] There may, however, be other reasons for a poor response of active distal colitis to treatment, including proximal constipation.

Proximal constipation: A characteristic pattern of motility may be observed in distal colitis, with slow mouth to caecum transit time, prolonged transit through uninvolved colon and rapid transit through inflamed distal colon.[19] This implies physiological changes in the small bowel and uninvolved colon, presumably through neuroendocrine or neuroimmune pathways. Whether such proximal constipation can delay resolution of distal inflammation is debatable, but it has been invoked as a cause of relapse in 10%.[20] Anecdotal experience suggests that relief of proximal constipation is associated with resolution of refractory disease. If there is visible faecal loading in the descending colon on a plain abdominal radiograph, it is worth giving a vigorous laxative (one to two sachets of Picolaxä or Fleet PhosphoSoda) after explaining the paradox of proximal constipation and diarrhoea in distal disease. Topical mesalazine should be continued, but if symptoms do not

TABLE 1
Differential diagnosis of refractory distal colitis.

Irritable bowel syndrome with bleeding haemorrhoids
Quiescent colitis with poor rectal compliance
Crohn's proctitis
Solitary rectal ulcer syndrome
Radiation proctitis
Infection (*Chlamydia* spp., *Herpes simplex*, opportunistic)
Salicylate-induced colitis
Neoplasia (carcinoma, lymphoma)

resolve within another two to four weeks, then intensive treatment is usually the best option.

Persistent disease activity: intensive treatment
Although more commonly a feature of extensive colitis, distal disease can present with a severe relapse (bloody stool frequency >six times daily, with either a pulse rate >90, temperature >37·8° C, haemoglobin <10·5 g/dL or ESR >30 mm/h). In one study of 51 episodes of severe colitis, 16% had distal disease.[21] This should be treated promptly by direct admission and intravenous steroids.

Intravenous steroids and cyclosporin: The real dilemma, however, is how best to manage patients with distal disease and continuing mild to moderate activity in spite of a course of oral steroids, topical salicylates and treatment of proximal constipation. Some gastroenterologists opt for further trials of topical therapy, often with alternative agents (see below). Such evidence as there is indicates that distal colitis in these circumstances is best treated as if it was more extensive or severe. In 39 patients with distal disease refractory to out-patient treatment with oral steroids and salicylates, remission was achieved by intensive treatment within a week in 90%.[22] This is an impressive and rapid response in otherwise refractory disease, and better than alternative topical therapies. Should the response be poor, the role of cyclosporin is debatable. It certainly has a place in severe distal colitis which is not responding to intravenous steroids, since colectomy may be avoided in a patient with limited disease.[23] The pattern of disease, however, must be taken into account. Relapse after cessation of cyclosporin is common, so cyclosporin should be reserved for those cases where there is the potential to change the pattern of disease by using azathioprine.

Reassessing the extent of disease: During admission for intensive treatment of refractory distal colitis it is appropriate to reassess the extent of disease, which may have become more extensive. Although the risk of proximal extension has conventionally been estimated at around 15%, it appears to be higher. In a retrospective study of 145 patients with distal colitis at presentation, disease extension proximal to the sigmoid was recorded in 36% at a median of six years, becoming extensive in 29%.[24] Using actuarial analysis, disease extension was predicted for 16% (CI 11–24%) at five years and 31% (CI 23–40%) ten years after diagnosis. Colonoscopy should therefore be performed during admission, which also helps exclude malignancy as a cause of refractoriness. Whilst the risk of colorectal cancer is not increased in distal colitis, sporadic cases may still occur.

MAINTAINING REMISSION IN DISTAL COLITIS

Once remission has been achieved, the next issue is how to prevent another relapse. Neither topical nor systemic steroids are effective, and in spite of advocating systemic steroids at an early stage to induce remission, the effect of long-term (>ten weeks) or recurrent courses (>two/year) on soft tissues and bone should be considered unacceptable. The options are an appropriate type and dose of aminosalicylate or immunosuppression.

Maintenance aminosalicylates
The main role of oral aminosalicylates is to maintain remission rather than treat active disease, but pharmacokinetic considerations influence the choice. Azo-bonded drugs are theoretically preferable in distal colitis, since luminal concentrations of 5-ASA are higher than with equivalent doses of slow-release mesalazine.[25] The most recent meta-analysis of maintenance therapy analysed 16 trials on 2,341 patients.[10] Sulphasalazine had a small but statistically significant benefit over mesalazine. The dose of amino-salicylate may also be more relevant in distal disease. When 198 patients were treated with 0·5 g, 1·0 g or 2·0 g olsalazine for 12 months, the highest dose was most effective in proctitis (90% remission, $p = 0·03$).[26] It was also most effective in those who had recently relapsed (<12 months) prior to the start of the trial. On a practical note, the tendency of olsalazine to cause diarrhoea can be used to therapeutic advantage if proximal constipation is associated with refractory distal colitis.

There are, however, very few comparative trials between the new salicylates. Olsalazine appears to be more effective than Asacol,[27] consistent with enhanced delivery of 5-ASA to the distal colon by olsalazine. Care must be taken in interpreting this study of 100 patients, because it finished early and had an unexpectedly high relapse rate (46% on Asacol at 12 months versus 34% on olsalazine). In another maintenance study of 99 patients, balsalazide 3 g/day was more effective than Asacol for controlling nocturnal symptoms, but the remission rate (58%) was identical at 12 months.[28] In practical terms, if remission cannot be maintained by olsalazine 2 g/day, then azathioprine is appropriate.

Thiopurines
Thiopurine therapy with azathioprine, or its metabolite 6-mercaptopurine, is indicated for those who relapse rapidly (<six weeks) after oral steroids and for those who relapse as the dose of prednisolone is decreased below 15mg/day.[29] This is as true for distal colitis as for those with more extensive disease. The standard dose for azathioprine is 2 mg/kg/day (1 mg/kg/day for 6-mercaptopurine) and several months' treatment is necessary for maximum effect. The main question is for how long thiopurines should be continued. In 67 patients in remission on azathioprine randomised to continue the drug or to placebo, 64% remained in remission on azathioprine at one year, compared to 41% on placebo ($p = 0·04$).[30] More recent data on 351 patients with ulcerative colitis treated with azathioprine showed a significant benefit in continuing therapy even after five years.[31] It is customary to continue oral salicylates with azathioprine, although there is no evidence that the combination is better than azathioprine alone.

Thiopurine intolerance: Unfortunately, up to 28% of patients cannot tolerate azathioprine, largely due to early intolerance (nausea, headaches, flu-like symptoms); myelosuppression affects fewer than five per cent.[31] In those with early intolerance, over 70% can tolerate 6-mercaptopurine,[32] which suggests that the imidazole ring cleaved from azathioprine during its metabolism causes some of the side-effects. The alternative is to use topical aminosalicylates to maintain remission. This is understandably less popular with patients, but may be effective and is an alternative to surgery. In five trials involving 182 patients given mesalazine suppositories or enemas for six to 24 months, remission was maintained in 54–80% compared to 15-20% on

TABLE 2
Selected trials of alternative therapies for distal colitis.

Agent	Proposed mechanism	Dose and duration	Design	N	Outcome	Reference
Anaesthetic gel	Neuroimmune modulation	Lignocaine (600 mg) daily. 6 wks	Open	22	12/22 'excellent', 4/22 'very good' response (refractory UC).	35
Arsenic	Uncertain	Acetarsol (500 mg) vs prednisolone (5 mg) suppositories. 2 wks	Random	20	9/10 clinical/endoscopic improvement (refractory distal colitis). Potential toxicity in 6/10 (1 wk) 2/10 (4 wks).	36
Bismuth compounds	Enhanced mucosal barrier ?Reduced bacterial adhesion	Bismuth carbomer (450 mg) enema vs 5-ASA (2 g) enema. 4 wks	Random	63	Bismuth 39% remission, 56% 5-ASA (trend in favour of 5=ASA, p = 0·16).	37
Cyclosporin enemas	T-cell immunosuppression 4 wks	Cyclosporin 350 mg vs placebo.	Random	40	Cyclosporin 40% improvement vs placebo 45%. Open trials in refractory distal UC more favourable.	38
Immunoglobulin G enemas	Immune response promoter	I gG enema.	Open	7	Ineffective. 1/7 improved.	39
Interleukin-10 enemas	?IL-10 deficiency in UC	IL-10 100 mcg enema for 10 days.	Open	3	Endoscopic response in refractory left-sided colitis.	40
Nicotine patch	Protective influence of smoking ?Neuroimmune	Transdermal nicotine (15-25 mg) vs placebo. 6 wks	Random	72	Nicotine 48% remission, placebo 24% (p = 0·03).	41
		Transdermal nicotine (15-25 mg) vs prednisolone (5-15 mg). 6 wks	Random	61	Nicotine 21% remission vs 47% prednisolone (p = 0·035), intention to treat. 11/31 nicotine withdrawals (side-effects).	42
Nicotine enema		Nicotine carbomer enemas (6 mg). 4 wks	Open	22	16/17 improved (previously unresponsive). 6 withdrawals.	43
Short-chain fatty acids	Epithelial nutrition	SCFA mixture. 6 wks	Open	10	5/10 responded well (refractory distal colitis).	44
		SCFA mixture vs placebo. 6 wks	Random	103	No difference in clinical or histological response.	45
Sucralfate	Enhanced mucosal barrier	Sucralfate (10 g) vs 5-ASA (2 g) vs placebo. 4wks	Random	50	5-ASA superior. Sucralfate no different from placebo.	46
Thromboxane A2 inhibitor	Inhibition of inflammatory mediator	Ridrogel (300 mg) vs prednisolone (30mg) enemas. 4wks	Random	40	Ridrogel 65% endoscopic remission vs prednisolone 75% (no difference).	47

placebo.[14] Compliance may be improved with intermittent therapy and mesalazine 1 g (Pentasa) suppositories three times a week maintained remission in 52% over one year, compared to 38% on placebo (p = 0·018).[33]

ALTERNATIVE THERAPIES

The choice of alternative therapies is large[34] (see Table 2[35-47]), but whilst this reflects the potential refractoriness of distal colitis, it also indicates a reluctance to use systemic treatment for limited disease. Using the approach outlined above, very few patients remain refractory. Some may consider it unnecessarily aggressive but it is, after all, much easier for the doctor to put up with a poor response to therapy than the patient. Nevertheless, some patients with limited and troublesome disease may achieve control by patiently persisting with topical therapy. The problem with these alternative therapies is that most are based on open studies or trials with insufficient power to detect a difference between treatments. The options do, however, illustrate innovative approaches with an insight into proposed mechanisms of disease. The choice really depends on local availability and personal preference, since many preparations have to be made up individually.

SURGERY

Surgery still has to be considered for some patients with distal colitis when active disease has not responded to intensive treatment, in those who cannot tolerate immunosuppression or when symptoms are affecting the quality of life or employment. Such a decision should never be precipitate and the decision is quite appropriately deferred until all medical options have been vigorously applied. A surgical option may best be raised when a patient is admitted for intensive treatment, if only to gauge the response. The opportunity to discuss stomas and pouches with an experienced stomatherapist is often appreciated by the patient and relatives, since it provides information even if this is subsequently unnecessary. Much depends on the individual patient's perception of disability caused by the disease and their attitude to surgery, but it also depends on the working relationship between the gastroenterologist and colorectal surgeon. A total colectomy has to be performed, usually with ileoanal pouch formation, because segmental resection leaves that part of the colon most affected and is almost invariably followed by relapse affecting previously normal bowel.

Operation rates for refractory colitis vary widely whatever the extent of disease. In Copenhagen, a higher proportion of patients come to surgery than in many centres, but represents the best population-based data available. Out of 498 patients with ulcerative colitis who had distal disease at presentation, 9% came to colectomy in the first year of diagnosis, followed by one per cent in subsequent years.[48] The outcome of surgery for distal colitis, however, is usually good. In 263 patients who had an ileoanal pouch at one French centre (1986–96), 27 had surgery for distal disease.[49] All but one patient were satisfied with the results and 25 out of 27 wished that they had had surgery sooner.

CONCLUSIONS

There is a pressing need for data to allow objective decisions to be made in the management of refractory distal colitis. On the current evidence, the algorithm (Figure 1) is a practical approach that helps clinical decision making. A combination of oral and topical therapy, salicylate suppositories as an adjunct to enemas, admission for intensive treatment and maintenance of remission with immunosuppression should be effective in the vast majority without resorting to alternative therapies or surgery.

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