Novel topical therapies for distal colitis

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Abstract
Distal colitis (DC) can be effectively treated with topical 5ASA agents. Suppositories target the rectum while enemas can reliably reach the splenic flexure. Used in combination with oral 5ASAs, the control of the inflammation is even more effective. Unfortunately, resistant DC does occur and can be extremely challenging to manage. In these patients, the use of steroids, immunosuppressants and the anti-tumor necrosis factor α agents are often required. These, however, can be associated with systemic side effects and are not always effective. The investigation of new topical therapeutic agents is thus required as they are rarely associated with significant blood drug levels and side effects are infrequent.

INTRODUCTION
Ulcerative colitis (UC) is a chronic inflammatory condition that is characterised by a life-long course of clinical remissions and exacerbations. Up to 15% of patients suffer a severe attack of their disease that requires hospitalisation at some stage during their life. While the management of these exacerbations have traditionally been dependent upon steroid therapy, a not insignificant proportion of patients fail to respond[1,2] and even in those patients who do respond, 25% of them are dependent on the use of steroids to maintain disease control[3]. Inflammation confined to the rectum occurs in approximately 25% of UC patients and, although this results in distressing symptoms including stool frequency, tenesmus, urgency and bleeding, it can often be managed within the community. Resistant ulcerative proctitis, however, can be extremely challenging to manage. When topical rectal 5ASA and steroid medications fail, oral agents including the 5ASAs, azathioprine (AZA)/6-mercaptopurine (6MP) and steroids may be employed but they do not always help. Infliximab, a medication that binds the proinflammatory cytokine tumor necrosis factor (TNF) α, can also be
effective in these patients with a clinical response in 68% and remission in about a third[13,14]. There are still, however, a significant proportion of UC patients who do not obtain clinical improvement, let alone remission, with these agents. It is for these patients that new and novel therapies require investigation.

**TACROLIMUS SUPPOSITORIES AND ENEMAS**

Tacrolimus and cyclosporine are classical calcineurin inhibitors that are widely used as immunosuppressive medications with some promising results observed in UC[7,8]. Calcineurin, or protein phosphatase 2B (PP2B), is a ubiquitously expressed cytosolic Ser/Thr protein phosphatase that is highly conserved in eukaryotes[9]. It has the ability to dephosphorylate a broad range of proteins and can regulate interleukin (IL)-2, IL-4 and interferon (IFN) \( \gamma \) expression as well as modulating the activity of transcription factors like NF-\( \kappa \)B[10]. Enhanced NF-\( \kappa \)B activity is well described in Crohn’s disease (CD) and UC and induces the proinflammatory cytokines IL-1\( \beta \), IL-6 and TNF\( \alpha \) expression. It is primarily through the reduction in the levels of these cytokines that clinical remission may be achieved.

The efficacy of oral tacrolimus has been examined in the management of medication resistant CD and UC. Unfortunately, the majority of these studies have been open labelled with only one randomised controlled trial reported in UC[12]. This demonstrated a short-term clinical improvement but without a significant increase in the remission rate, potentially due to low patient numbers. Despite this, there are numerous open labelled studies in both UC and CD that suggest efficacy in the short term and with promising long-term data[13-17]. The evidence would suggest, however, that the blood trough level should be at least 10 \( \mu g/L \) in order to achieve the best efficacy (therapeutic range 5-20 \( \mu g/L \)), but the higher the trough level, the more likely a patient will suffer an adverse effect. These, unfortunately, can be numerous and include hypertension, nausea and diarrhea, hematological abnormalities and renal impairment[18]. Increased rates of skin cancers is also a concern[19] supported by animal studies[20]. Overall assessment of the current published data in inflammatory bowel disease (IBD), therefore, suggests some efficacy but it is unclear if tacrolimus will induce remission and it can be associated with serious adverse effects[21].

Topical tacrolimus has been effective in the treatment of perioral and perineal inflammation in paediatric CD patients with resolution of symptoms in 75%[22]. Work examining topical perianal tacrolimus therapy in adult CD patients also demonstrated clinical efficacy[23] and although tacrolimus is absorbed well transdermally[24], only low trough levels of tacrolimus are detected in the blood[25]. In these preliminary studies, the use of topical tacrolimus was associated with few side effects. Long-term topical use, as with oral formulations, may be associated with an increased risk of skin cancer formation. Epidemiological evidence, however, would suggest that the risk is low and localised to the tacrolimus-treated sun-exposed skin[26].

Two recent studies have started to investigate the efficacy of rectal tacrolimus in resistant distal colitis. In the first, 8 UC patients with inflammation to a maximum of 30 cm from the anus were included. All patients had demonstrated disease resistant to numerous medications both standard and experimental[27]. Following 4 wk of topical tacrolimus, 75% (6/8) of patients achieved clinical remission with oral corticosteroids ceased in the majority of patients. The second study examined the use of topical tacrolimus in 19 patients with resistant distal colitis. Twelve patients received tacrolimus suppositories and 7 tacrolimus enemas. Clinical and histological improvement was observed in 10 of 12 patients treated with tacrolimus suppositories but there was no significant benefit in the majority of patient receiving the tacrolimus enemas[28], potentially due to the lower concentration of tacrolimus at the mucosal surface with the enema preparation. No major side effects were reported in either of the studies and the preparations were well tolerated. As these studies demonstrate encouraging results in a difficult-to-treat patient population, further randomised placebo controlled trials are warranted.

**CYCLOSPORINE ENEMAS**

The use of intravenous cyclosporine (CsA) has been well described as an effective rescue therapy in up to 80% of acute severe steroid-refractory UC patients[29,30]. The intravenous therapy is then followed by oral CsA for a period of 3 mo while the patients are transitioned onto long-term immunomodulator therapy with AZA/6MP[31]. Despite the use of these agents, however, many patients will relapse and require colectomy within 12 mo[30,32,33]. Concerns over the safety profile of CsA, even at a low oral dose[34] has, however, resulted in a reluctance for some clinicians to use this medication.

The topical use of CsA as an enema in distal UC was first described in 1989[35]. The bioavailability of CsA was not measurable for both the oil and water suspension enemas suggesting that the systemic absorption of CsA following retention enemas is negligible and unlikely to be associated with systemic side effects[36,37]. Two open labeled studies have been reported in the management of treatment-resistant left-sided UC but none has specifically investigated proctitis. In the first, of 10 patients with left-sided UC, 50% responded with 350 mg cyclosporine nightly enemas for 4 wk[38]. The second study observed that 7 of 12 UC patients improved with 250 mg CsA administered daily as a retention enema[39]. The single randomized placebo-controlled trial of CsA enemas in left-sided ulcerative colitis, however, demonstrated that at 4 wk, 40% of patients receiving CsA responded compared with 45% of those who received placebo[40]. This is similar to the findings for tacrolimus enemas and may also be related to the concentration of the medication at the mucosal surface. To date, the use of CsA suppositories has not been investigated.
**BUTYRATE ENEMAS**

NF-κB activation is important for the activation of inflammation in UC. Butyrate, a short chain fatty acid (SCFA), demonstrates anti-inflammatory effects through the decrease in the translocation of NF-κB into the nucleus of lamina propria macrophages\[^{48}\]. Inflammation in UC may be due, in part, to a state of energy deficiency of the colonic mucosa secondary to impaired SCFA production, uptake or utilization, while butyrate appears to be the SCFA that is most actively metabolized by the colonic mucosa. The use of butyrate enemas may, therefore, potentially reverse any state of energy deficiency.

Examination of butyrate enemas in patients suffering distal UC demonstrated promising results in the initial open labelled studies. In the first of 2, 6 of 10 patients treated with nightly butyrate enemas responded while 4 obtained clinical remission \[^{41}\]; in the second, out of 9 patients there was endoscopic and histological improvement in 7 following 2 wk of therapy\[^{49}\]. In a single-blinded placebo-controlled study, 10 UC patients with distal colitis unresponsive or intolerant to standard therapy received 2 wk of butyrate enemas and then 2 wk of placebo in random order. Following butyrate irrigation, stool frequency decreased while the passage of blood ceased in 9 of 10 patients\[^{50}\].

Unfortunately, the randomized, double blind, placebo-controlled studies have been less impressive. The first investigated 40 patients with mild to moderate distal colitis but there was no statistical difference detected between the number of patients who improved with butyrate enemas (n = 14) compared to placebo (n = 5)\[^{50}\]. A second study of 38 patients also failed to demonstrate a better clinical outcome with a clinical improvement observed in 37% of butyrate-treated compared to 47% of placebo-treated patients\[^{40}\]. A third 6-wk double-blind, placebo-controlled trial of SCFA enemas that included sodium butyrate (40 mmol/L), in 91 patients only demonstrated an improvement in 33% of SCFA enemas-treated patients compared to 20% of those who received placebo. Again, these were not significantly different\[^{40}\]. Thus, although all the studies commented that there was some efficacy with the use of butyrate in a subset of patients and to obtain as response there may be a need for prolonged mucosa contact, butyrate enemas do not appear to be superior to placebo in the treatment of distal colitis.

**ECABET SODIUM ENEMAS**

Ecabet sodium (ES) is a 12-sulfo dehydroabietic acid monosodium salt derived from an ingredient found in pine resin. It is primarily a non-absorbable protectant and to proteins in a non-specific manner as the amount bound is almost constant regardless of the ES concentration. ES binding, however, does appear to be pH dependant with greater binding at low pH due to a higher hydrophobicity. Increased binding may also occur through the interaction between the negative charge of the dissociated sulfate moiety of ES at low pH and the positive charge of the proteins\[^{56}\].

Clinical studies have demonstrated efficacy for ES in the management of gastritis and gastric ulceration due to its affinity for adherence to the gastric mucosa and to fibrinogen located on the gastric ulcer base\[^{47}\]. This was also observed to be the case for the rat model of colitis [following 9 d ingestion of dextran sodium sulphate (DSS) added to the drinking water]. In this model, rectally administered ES bound at greater rates to damaged mucosa than to the normal intestinal lining\[^{49}\]. Two open labelled studies have also investigated the utility of ES in the management of distal UC. In the original study, 7 patients demonstrated clinical, endoscopic and histological remissions following twice daily rectal administration for 2 wk\[^{59}\]. In the second study the findings were less impressive with all six patients responding to ES administration following up to 7 wk of therapy but none achieved remission\[^{51}\]. High binding of ES to sites of intestinal inflammation was again demonstrated in the first of these studies suggesting that, as for its proposed primary mode of action in gastric inflammation, the clinical benefit of ES in colonic inflammation can be attributable to its role as a coating agent.

Mucin is the major component of the intestinal mucus barrier and is produced by intestinal goblet cells. Goblet cell loss, diminished mucin production and epithelial cell damage accompany the histological changes observed with the active inflammation associated with UC. Loss of goblet cells and attenuation of the mucus protective barrier has also been observed in murine models of colitis, including mice with mutations in the MUC2 gene that have a sub-optimal mucosal barrier and are more susceptible to the colitis induced by luminal toxins\[^{52}\]. These animal models develop chronic transmural enterocolitis due to an aberrant immune response against normal enteric pathogens. When animals, however, are maintained in germ-free conditions, colitis does not develop\[^{53-55}\]. In these animal models, it is the combination of a breakdown in the protective barrier between the colon luminal contents and intestinal mucosa with the presence of an intact colonic flora that promotes intestinal inflammation. As ES has the ability to provide a barrier against the translocation of luminal antigens into the intestinal wall, it is thus not unreasonable that a beneficial effect following its use may be observed in patients with resistant proctitis. Further studies, however, are still required to adequately assess the role, function and efficacy of ES in the topical management of distal colitis.

**LIDOCAINE ENEMAS**

Lidocaine was first proposed in 1988 as a treatment of DC based on the hypothesis that hyper-reactivity of the autonomic nerves may play a role in the pathogenesis of UC\[^{34}\]. Efficacy has since been shown to reduce the level of acute inflammation in the trinitrobenzene sulfonic acid (TNBS) and DSS rat models of colitis\[^{47,57}\]. The initial open-labelled study into UC investigated the use of 2% lidocaine gel (400 mg twice daily) and included 28 patients

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with proctitis, all of who responded clinically within 3-12 wk. The cohort also included 49 patients with DC and of these, 41 responded following 6-34 wk of therapy. Despite these impressive results, however, no further studies have been published.

**EPIDERMAL GROWTH FACTOR ENEMAS**

Epidermal growth factor (EGF) is a 1207-amino-acid precursor that is found in the gastric juices (500 ng per liter)\(^6\). As it can stimulate healing\(^6\) and it has warranted investigation with preliminary human studies suggesting that the topical use of EGF can enhance skin wound healing\(^6\) while systemic EGF can be beneficial in the management of necrotizing enterocolitis\(^6\). In the proximal gastrointestinal tract, however, EGF is cleaved to a less active form and under physiological conditions very little luminal EGF ever reaches the colon. Circulating levels of EGF are also low and not readily available to the gastrointestinal mucosa.

The use of EGF enemas (5 mg in 100 mL) in the management of left-sided UC was assessed in a randomized, double-blind placebo-controlled trial in 24 patients. After 2 wk of therapy, all patients who received EGF had improved with 10 of 12 (83%) in remission compared with 1 of 12 in the control group (8%, P < 0.001). The endoscopic and histological scores were all significantly better in the EGF than placebo group\(^6\). Unfortunately, despite these impressive results no further investigations into the use of EGF in distal colitis have been undertaken or have not yet been published.

**REBAMIPIDE ENEMAS**

Rebamipide [2-(4-chlorobenzoylamino)-3-[2-[(1H)-quinoxalin-4-y1]-propionic acid] is able to stimulate the production of endogenous prostaglandins and accelerate the healing process\(^6\). It also reduces the intestinal inflammation in both the TNBS and DSS rat models of colitis\(^6\). The first open-labelled study investigating its use included 11 patients with steroid resistant/dependant proctitis or DC\(^6\). Histological improvement and clinical remission in 9 patients was demonstrated after 12 wk of twice daily administration of 150 mg rebamipide in 1.5% carboxymethyl cellulose at pH 6.34. A further open-labelled study demonstrated clinical remission in 5 of 16 patients while another 2 demonstrated a marked improvement after 4 wk of therapy\(^6\). The final open-labelled study treated 20 patients for 3 wk with 11 achieving clinical remission and 16 responding endoscopically\(^6\). As yet, however, no randomized double-blind, placebo-controlled studies have been undertaken.

**NICOTINE ENEMAS**

As UC is largely a disease of non-smokers, the use of nicotine in its management has been investigated. It has several modes of action that could potentially reduce intestinal inflammation including effects on the gut motility\(^7\) and immune function\(^7\). The open labelled use of a nightly enema containing 6 mg of nicotine for 4 wk was examined in 17 UC patients. All were non-smokers and 16 of 17 improved their St Mark's score, stool frequency and urgency improved in 12 patients and the endoscopic and histological scores improved in 10\(^2\). The only randomized placebo-controlled study that investigated the use of 6 mg nicotine enemas for 6 wk in 104 patients with active UC, however, demonstrated no significant benefit with nicotine over placebo enemas with clinical remission achieved in 27% patients on active treatment and 33% on placebo\(^7\).

**ARSENIC ENEMAS**

The use of arsenic suppositories for the management of resistant proctitis was first described over 30 years ago\(^6\) but the mechanism of action remains unknown. However, there has only been a single small open labeled study that investigated the use of Acetarsol® suppositories twice a day for 4 wk in 10 patients. These suppositories contain 68 mg of 3-acetamido-4-hydroxyphenylarsonic acid which is organic arsenic. In 9 of these patients, the symptoms and endoscopic signs of proctitis resolved within 2 wk. Despite the promising findings of efficacy, in 6 patients the arsenic was absorbed systemically with the total inorganic arsenic blood level considered to be in the hazardous range\(^6\). Unfortunately, despite anecdotal reports of efficacy, no further studies have been published on the use of this agent in distal UC.

**THROMBOXANE ENEMAS**

Thromboxanes are produced in excess in the inflamed intestinal mucosa of IBD patients and in isolated intestinal cells and peripheral blood mononuclear cells in patients with CD. Inhibitors of thromboxane synthesis have also been shown to reduce the release of TNFα by human macrophages. The open labeled use of the thromboxane synthase inhibitor and receptor antagonist, Ridogrel®, has been investigated in 11 patients as an enema in left-sided UC. Mucosal thromboxane levels were reduced in all patients but the level of the anti-inflammatory mediators IL-6 and TNFα were unchanged. Five patients responded clinically to the treatment but this was not always associated with a decrease in the endoscopic or histological scores of inflammation\(^7\). This preliminary study may suggest some efficacy to this therapy but as yet no further studies have been undertaken.

**CONCLUSION**

When topical 5ASA and steroid medications fail, distal ulcerative colitis and proctitis can be extremely challenging to manage. Oral agents and anti-TNFα therapy may be employed but they do not always help. The use of oral medications is also frequently associated with systemic
side effects while the use of topical agents is rarely associated with significant systemic drug levels. Unfortunately, despite there being a number of potentially useful topical therapeutic agents reported in the literature, medications like tacrolimus suppositories and tacrolimus, eucabt sodium, arsenic, lidocaine, rebamipide and Ridogrel® enemas have only demonstrated clinical efficacy in open-labelled studies. In those novel agents that have undergone randomised studies, butyrate, cyclosporine and nicotine enemas did not demonstrate efficacy above that observed for placebo, while, despite impressive evidence for epidermal growth factor enemas, there has only been a single small study. It does appear, however, that the mucosal medication concentration and/or contact time may be important for these agents to work suggesting that perhaps enemas are not the best method of administration and that suppositories could be more appropriate. It is, however, more than obvious that further investigation is required before any of these agents can be considered as routine in the management of resistant ulcerative proctitis and distal colitis.

REFERENCES

1. Järnerot G, Rolny P, Sandberg-Gertzén H. Intensive intravenous treatment of ulcerative colitis. *Gastroenterology* 1985; 89: 1005-1013
2. Truelove SC. Ulcerative colitis. Medical management. *Br Med J* 1971; 1: 651-653
3. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001; 121: 255-260
4. Rutgeerts P, Sandborn WJ, Feagan BG, Reinsch W, Olson A, Johanss J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Inflammation for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; 353: 2462-2476
5. Willett RP, Lawrance IC. Use of infliximab in the prevention and delay of colectomy in severe steroid dependent and refractory ulcerative colitis. *World J Gastroenterol* 2008; 14: 2544-2549
6. Pearce CB, Lawrance IC. Careful patient selection may improve response rates to infliximab in inflammatory bowel disease. *J Gastroenterol Hepatol* 2007; 22: 1671-1677
7. Ng SC, Kamm MA. Review article: New drug formulations, chemical entities and therapeutic approaches for the management of ulcerative colitis. *Aliment Pharmacol Ther* 2008; 28: 815-829
8. Ng SC, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. *Inflamm Bowel Dis* 2009; 15: 935-950
9. Klee CB, Ren H, Wang X. Regulation of the calmodulin-stimulated protein phosphatase, calcineurin. *J Biol Chem* 1998; 273: 13367-13370
10. Serfling E, Berberich-Siebelt F, Chuvpilo S, Jankevics E, Kleinhessling S, Twardzik T, Avots A. The role of NF-AT transcription factors in T cell activation and differentiation. *Biochem Biophys Acta* 2000; 1498: 1-18
11. Frantz B, Nordtby EC, Boren G, Steffen N, Paya CV, Kincaid RL, Tocci MJ, O’Keefe SJ, O’Neill EA. Calcineurin acts in synergy with PMA to inactivate I kappa B/MAD3, an inhibitor of NF-kappa B. *EMBO J* 1994; 13: 861-870
12. Ogata H, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y, Hibi T. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; 55: 1255-1262
13. Baumgart DC, Pintoff JP, Sturm A, Wiedemann B, Dignass AU. Tacrolimus is safe and effective in patients with severe steroid-refractory or steroid-dependent inflammatory bowel disease—a long-term follow-up. *Am J Gastroenterol* 2006; 101: 1048-1056
14. Baumgart DC, Wiedemann B, Dignass AU. Rescue therapy with tacrolimus is effective in patients with severe and refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; 17: 1273-1281
15. Ierardi E, Principi M, Francavilla R, Pisani A, Rendina M, Ingrassio M, Guglielmi FW, Panella C, Francavilla A. Oral tacrolimus long-term therapy in patients with Crohn’s disease and steroid resistance. *Aliment Pharmacol Ther* 2001; 15: 371-377
16. Ierardi E, Principi M, Francavilla R, Pisani A, Rendina M, Panella C, Francavilla A. Long-term tacrolimus: a promising therapeutic approach for Crohn’s disease. *Transplant Proc* 2001; 33: 2107-2109
17. Ng SC, Arebi N, Kamm MA. Medium-term results of oral tacrolimus treatment in refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007; 13: 129-134
18. Perera GK, Child FJ, Heaton N, O’Grady J, Higgins EM. Skin lesions in adult liver transplant recipients: a study of 100 consecutive patients. *Br J Dermatol* 2006; 154: 868-872
19. Niwa Y, Terashima T, Sumi H. Topical application of the immunosuppressant tacrolimus accelerates carcinogenesis in mouse skin. *Br J Dermatol* 2003; 149: 960-967
20. Baumgart DC, Macdonald JK, Feagan B. Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. *Cochrane Database Syst Rev* 2008; CD007216
21. Casson DH, Eltumi M, Tomlin S, Walker-Smith JA, Murch SH. Topical tacrolimus may be effective in the treatment of oral and perineal Crohn’s disease. *Gut* 2000; 47: 436-440
22. Hart AL, Plamondon S, Kamm MA. Topical tacrolimus in the treatment of perianal Crohn’s disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007; 13: 245-253
23. Lauerna AI, Surber C, Maibach HI. Absorption of topical tacrolimus (FK506) in vitro through human skin: comparison with cyclosporin A. *Skin Pharmacol Phsyiol* 1995; 10: 230-234
24. Rustin MH. The safety of tacrolimus ointment for the treatment of atopic dermatitis: a review. *Br J Dermatol* 2007; 157: 861-873
25. Albert MH, Becker B, Schuster FR, Klein B, Binder V, Adam K, Nienhoff C, Führer M, Borkhardt A. Oral graft vs. host disease in children—treatment with topical tacrolimus ointment. *Pediatr Transplant* 2007; 11: 306-311
26. Yarosh DB, Canning MT, Teicher D, Brown DA. After sun reversal of DNA damage: enhancing skin repair. *Mutat Res* 2005; 571: 57-64
27. Lawrance IC, Copeland TS. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. *Aliment Pharmacol Ther* 2008; 28: 1214-1220
28. van Dieren JM, van Bodegraven AA, Kuipers EJ, Bakker EN, Poen AC, van Dekken H, Nieuwenhuis EE, van der Woude CJ. Local application of tacrolimus ointment in recalcitrant perianal Crohn’s disease. *Aliment Pharmacol Ther* 2007: 245-253
29. Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; 330: 1841-1845
30. Moskovitz DN, Van Assche G, Maenhout B, Arts J, Ferrante M, Vermeire S, Rutgeerts P. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2006; 8: 764-765
31. Bamba S, Tsujikawa T, Inatomi O, Nakahara T, Koizumi Y, Saitoh Y, Sasaki M, Fujiyama Y, Andoh A. Factors affecting the efficacy of cyclosporin A therapy for refractory ulcerative colitis. *J Gastroenterol Hepatol* 2010; 25: 494-498
32. Campbell S, Travis S, Jewell D. Cyclosporin use in acute ulcerative colitis: a long-term experience. *Eur J Gastroenterol Hepatol* 2006; 18: 1214-1220
Lawrence IC. Topical therapies for proctitis

2005; 17: 79-84

Arts J, D'Haeens G, Zeegers M, Van Assche G, Hiele M, D'Hoore A, Penninckx F, Vermeire S, Rutgers P. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. Inflamm Bowel Dis 2004; 10: 73-78

Mathews D, Mathews J, Jones NP. Low-dose cyclosporine treatment for sight-threatening uveitis: efficacy, toxicity, and tolerance. Indian J Ophthalmol 2010; 58: 55-58

Ranzi T, Campanini MC, Vello P, Quarto di Polo F, Bianchi P. Treatment of chronic proctosigmoiditis with cyclosporin enemas. Lancet 1989; 2: 97

Sandborn WJ, Strong RM, Forsland SC, Chase RE, Cutler RE. The pharmacokinetic and colonic tissue concentrations of cyclosporine after i.v., oral, and enema administration. J Clin Pharmacol 1991; 31: 76-80

Sandborn WJ, Tremaine WJ, Schroeder KW, Steiner BL, Batts KP, Lawson GM. Cyclosporine enemas for treatment-resistant, mildly to moderately active, left-sided ulcerative colitis. Am J Gastroenterol 1993; 88: 640-645

Winter TA, Dalton HR, Merritt NN, Campbell A, Jessell DP. Cyclosporin A retention enemas in refractory distal ulcerative colitis and ‘pouchitis’. Scand J Gastroenterol 1993; 28: 701-704

Sandborn WJ, Tremaine WJ, Schroeder KW, Batts KP, Lawson GM, Steiner BL, Harrison JM, Zimmemeir AR. A placebo-controlled trial of cyclosporine enemas for mildly to moderately active left-sided ulcerative colitis. Gastroenterology 1994; 106: 1429-1435

Lührs H, Gerke T, Müller JC, Melcher R, Schaubier J, Boxberger F, Scheppach W, Menzel U. Butyrate inhibits NF-κappaB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 2002; 37: 458-466

Steinhart AH, Brzezinski A, Baker JP. Treatment of refractory ulcerative proctosigmoiditis with butyrate enemas. Am J Gastroenterol 1994; 89: 179-183

Vernia P, Cittadini M, Caprilli R, Torsoli A. Topical treatment of refractory distal ulcerative colitis with 5-ASA and sodium butyrate. Dig Dis Sci 1995; 40: 305-307

Scheppach W, Sommer H, Kirchner T, Paganelli GM, Bartram C, Christl S, Richter F, Dusel G, Kasper H. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. Gastroenterology 1992; 103: 51-56

Vernia P, Marcheggiano A, Caprilli R, Frieri G, Corroa G, Valpiani D, Di Paolo MC, Pauluzzi P, Torsoli A. Short-chain fatty acid topical treatment in distal ulcerative colitis. Aliment Pharmacol Ther 1995; 9: 309-313

Steinhart AH, Hiruki T, Brzezinski A, Baker JP. Treatment of left-sided ulcerative colitis with butyrate enemas: a controlled trial. Aliment Pharmacol Ther 1996; 10: 729-736

Breuer RI, Soergel KH, Lashner BA, Christ ML, Hanauer SB, Vanagunas A, Harig JM, Keshavarzian A, Robinson M, Sellin JH, Weinberg D, Vidican DE, Femail KL, Rademaker AW. Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. Gut 1997; 40: 485-491

Flanagan WM, Courtbeny B, Bram RJ, Crabtree GR. Nuclear association of a T-cell transription factor blocked by FK-506 and cyclosporin A. Nature 1991; 352: 803-807

Ito Y, Onoda Y, Nakamura S, Tagawa K, Fukushima T, Sugawara Y, Takaito O. Effects of the new anti-ulcer drug ebcab sodium (TA-2711) on pepsin activity. II. Interaction with sub-strate protein. Jpn J Pharmacol 1993; 62: 175-181

Noto T, Yamada H, Inui T, Okuyama K, Watanable A, Kimura I, Nagasaki M. Therapeutic effects of ebcab sodium, an antiulcer drug, on dextran sodium sulfate-induced ulcerative colitis in rats. Dig Dis Sci 2005; 50: 922-927

Kono T, Nomura M, Kasai S, Kohgo Y. Effect of ebcab sodium enema on mildly to moderately active ulcerative proctosigmoiditis: an open-label study. Am J Gastroenterol 2001; 96: 793-797

Monteleone G, Caprioli F. Drug evaluation: TA-2711E in the treatment of active distal ulcerative colitis. Curr Opin Investig Drugs 2007; 8: 423-428

Heazlewood CK, Cook MC, Eri R, Price GR, Tauro SB, Taupin D, Thornton DJ, Png CW, Crockford TL, Connolly R, Adams R, Kato M, Nelms KA, Hong NA, Florin TH, Goodnow CC, McCuekin MA. Aberrant mucin assembly in mice causes endoplasmic reticulum stress and spontaneous inflammation resembling ulcerative colitis. PLoS Med 2008; 5: e54

Powrie F, Leach MW. Genetic and spontaneous models of inflammatory bowel disease in rodents: evidence for abnormalities in mucosal immune regulation. Ther Immunol 1995; 2: 115-123

Elson CO, Sartor RB, Tennyson GS, Riddell RH. Experimental models of inflammatory bowel disease. Gastroenterology 1995; 109: 1344-1367

Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. Gastroenterology 2004; 126: 1620-1633

Björk S, Ahlman H, Dahlström A. Lignocaine and ulcerative proctitis. Lancet 1988; i: 1330

Björk S, Jonsiche E, Dahlström A, Ahlman H. Influence of topical rectal application of drugs on dextran sulfate-induced colitis in rats. Dig Dis Sci 1997; 42: 824-832

McCafferty DM, Sharkey KA, Wallace JL. Beneficial effects of local or systemic lidocaine in experimental colitis. Am J Physiol 1994; 266: G560-G567

Playford RJ, Marchbank T, Calnan DP, Calam J, Royston P, Batten JJ, Hansen HF. Epidermal growth factor is digested to smaller, less active forms in acidic gastric juice. Gastroenterol 1995; 108: 92-101

Playford RJ. Peptides and gastrointestinal mucosal integrity. Gut 1995; 37: 595-597

Brown GL, Nanney LB, Griffen J, Cramer AB, Yancey JM, Curtissinger LJ 3rd, Holtzin L, Schultz GS, Jurkiewicz MJ, Lynch JB. Enhancement of wound healing by topical treatment with epidermal growth factor. N Engl J Med 1989; 321: 76-79

Sullivan PB, Brutton MJ, Tabara ZB, Goodlad RA, Lee CY, Wright NA. Epidermal growth factor in necrotising enteritis. Lancet 1991; 338: 53-54

Sinha A, Nightingale J, West KP, Berlanga-Acosta J, Playford RJ. Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. N Engl J Med 2003; 349: 350-357

Genta RM. Review article: the role of rebamipide in the management of inflammatory disease of the gastrointestinal tract. Aliment Pharmacol Ther 2003; 18 Suppl 1: 8-13

Kishimoto S, Haruma K, Tari A, Sakurai K, Nakano M, Nakagawa Y. Rebamipide, an antiulcer drug, prevents DSS-induced colitis formation in rats. Dig Dis Sci 2000; 45: 1608-1616

Zea-Iriarte WL, Makiyama K, Goto S, Murase K, Urata Y, Sekine I, Hara K, Kondo T. Impairment of antioxidants in colonic epithelial cells isolated from trinitrobenzene sulphonic acid-induced colitis rats. Protective effect of rebamipide. Scand J Gastroenterol 1996; 31: 985-992

Miyata M, Kasugai K, Ishikawa T, Kakumu S, Onishi M, Mori T. Rebamipide enemas-new effective treatment for patients with corticosteroid dependent or resistant ulcerative colitis. Dig Dis Sci 2005; 50 Suppl 1: S119-S123

Makiyama K, Takahata F, Hamamoto T. Efficacy of rebamipide enemas in active distal ulcerative colitis and proctitis: a prospective study report. Dig Dis Sci 2005; 50: 2323-2329

Furuta R, Ando T, Watanabe O, Maeda O, Ishiguro K, Ina K, Kusugami K, Goto H. Rebamipide enema therapy as a treatment for patients with active distal ulcerative colitis. J Gastroenterol Hepatol 2007; 22: 261-267

Green JT, McKirdy HC, Rhodes J, Thomas GA, Evans BK. Intra-luminal nicotine reduces smooth muscle tone and contractile activity in the distal large bowel. Eur J Gastroenterol Hepatol 1999; 11: 1299-1304
Lawrance IC. Topical therapies for proctitis

71 Geng Y, Savage SM, Razani-Boroujerdi S, Sopori ML. Effects of nicotine on the immune response. II. Chronic nicotine treatment induces T cell anergy. *J Immunol* 1996; 156: 2384-2390

72 Green JT, Thomas GA, Rhodes J, Williams GT, Evans BK, Russell MA, Feyeraebend C, Rhodes P, Sandborn WJ. Nicotine enemas for active ulcerative colitis—a pilot study. *Aliment Pharmacol Ther* 1997; 11: 859-863

73 Ingram JR, Thomas GA, Rhodes J, Green JT, Hawkes ND, Swift JL, Srivastava ED, Evans BK, Williams GT, Newcombe RG, Courtney E, Pillai S. A randomized trial of nicotine enemas for active ulcerative colitis. *Clin Gastroenterol Hepatol* 2005; 3: 1107-1114

74 Connell AM, Lennard-Jones JE, Misiewicz JJ, Baron JH, Jones FA. Comparison of acetarsol and prednisolone-21-phosphate suppositories in the treatment of idiopathic proctitis. *Lancet* 1965; 1: 238

75 Forbes A, Britton TC, House IM, Gazzard BG. Safety and efficacy of acetarsol suppositories in unresponsive proctitis. *Aliment Pharmacol Ther* 1989; 3: 553-556

76 Auwerda JJ, Zijlstra FJ, Tak CJ, van den Ingh HF, Wilson JH, Ouwendijk R. Ridogrel enemas in distal ulcerative colitis. *Eur J Gastroenterol Hepatol* 2001; 13: 397-400

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