New treatments for inflammatory bowel disease

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INTRODUCTION

Although inflammatory bowel disease (IBD) is apparently still relatively rare in the East, evidence from Hong Kong suggests that over recent decades the incidence of both ulcerative colitis (UC) and Crohn’s disease (CD) may be rising there[1-3]. Indeed, it seems likely that as the prevalence of enteric infections falls, and urbanisation and diagnostic awareness increase, IBD will become increasingly common in Asia, as it has in the last fifty years in Europe and North America. It therefore seems appropriate to review advances in the medical therapy of these often refractory diseases.

In this paper, I shall not attempt to review extensive earlier evidence about the efficacy of corticosteroids, aminosalicylates or, in patients refractory to these drugs, immunosuppressive agents; nor shall I discuss the role of surgery. Furthermore, rather than describing the management of the “whole” patient with IBD[4,5], I shall concentrate primarily on drugs which have recently gained an established place in, or appear very promising for, the treatment of IBD. I shall also outline the use of liquid formula diets in active CD, and mention the possible but unproven place of traditional medical modalities.

At the outset, it is worth emphasizing some of the problems encountered in the evaluation of new treatments for IBD. UC and CD have fluctuating courses which depend on both site and extent of disease, as well as, in CD, previous surgery and the time since the most recent relapse. In both diseases, objective measurement of disease activity and definition of trial endpoints is difficult. In CD, for example, measures of disease activity, such as the Crohn’s disease activity index (CDAI), colonscopic appearances and laboratory variables, do not always move in parallel[6].

In addition to these difficulties, the design, conduct and interpretation of trials in IBD is complicated by the size and variability of the placebo response[7], the too frequent use of small numbers of patients with consequent Type II statistical errors, and the confounding effects of concurrent or recently discontinued therapy.

Finally, none of the numerous experimental animal models of bowel inflammation resembles human IBD sufficiently closely to enable valid extrapolation of results in such studies to the clinical arena. A possible exception to this generalisation is the spontaneous colitis to which the cotton-top tamarin in captivity is prone[8], but the animal’s rarity and expense prevents its utilisation for large scale therapeutic trials. In this review, therefore, attention will be focussed primarily on results obtained in human studies.

AETIOPATHOGENESIS OF IBD

Although the aetiology of IBD remains obscure, recent studies have begun to shed light on its pathogenesis. In brief, it appears that an initiating factor, for example a microbial or dietary product or antigen, triggers an inappropriately severe and prolonged intestinal mucosal inflammatory response in genetically predisposed individuals[9]. The inflammatory response is amplified and perpetuated by recruitment of leucocytes from the gut vasculature which, with upregulation of the expression of nuclear transcription factors such as NFkB[10], leads to excessive release locally of cytokines[9], eicosanoids[11], reactive oxygen metabolites[12] and other mediators. In CD, in particular, a procoagulant diathesis and multifocal granulomatous intestinal microinfarction may occur early in the disease process[13]. Elucidation of the pathogenesis of IBD has improved our understanding of the possible modes of action of conventional treatment (Table 1) and has led to the development of entirely new therapeutic approaches, to be discussed in the second half of this review (Table 2).

NEW FORMULATIONS AND APPLICATIONS OF EXISTING DRUGS

Corticosteroids (Table 1)

Corticosteroids are the most useful conventional agents in the treatment of active IBD, whether given orally, intravenously or topically[4,5]. They have multiple potentially beneficial actions on the...
inflammatory process, but which of these is, or are, of predominant importance in IBD is unclear. The anti-inflammatory actions of steroids include inhibition of leucocyte migration and activation; inhibition of the expression of cellular adhesion molecules; suppression of synthesis of cytokines (interleukins-1, -2, -6, -8 and tumour necrosis factor (TNF)), at least in part by inhibition of the activation of NFkB; reduction of release of lipid mediators (leucotrienes, thromboxanes, prostaglandins and platelet activating factor (PAF)); and inhibition of phospholipase A2, cyclooxygenase 2 and inducible nitric oxide synthase.

The numerous side-effects of systemic corticosteroids, particularly when given longterm (e.g. moon face, acne, purpura, dysphoria, opportunistic infection, hypertension, diabetes mellitus, weight gain, osteopaenia and growth retardation in children), have prompted a search for safer for mutations. To this end, a number of corticosteroid preparations have recently been assessed which when given orally are either poorly absorbed from the gut or very rapidly metabolised in the intestinal wall or liver: one of these, budesonide, has so far achieved clinical application.

When given in an oral controlled ileal release (CR) formulation to patients with active ileocaecal CD, budesonide was not significantly less effective than prednisolone in inducing remission in one study[14] and substantially better than placebo in another[15]. Side-effects were much fewer in patients given budesonide CR than prednisolone, as was adrenal suppression assessed by measurement of plasma cortisol levels[14]. When evaluated for maintenance of remission over 12 months in CD, budesonide CR delayed the onset of relapse when compared to placebo, but overall relapse rates at 1 year (60-70%) were, disappointingly, not improved[16,17]. In a trial in patients with UC, an oral colonic release preparation of budesonide showed benefit similar to that obtained with prednisolone in patients with active disease; particularly if extensive, disease; improved efficacy for patients with left-sided disease may depend upon the development of formulations providing even more delayed release of the active drug, or the use of higher doses[18]. Further studies are needed to clarify the role of oral budesonide in IBD. In particular, we require reassurance that to achieve a clinical result equivalent to that of prednisolone, it will not be necessary to use so great a dose of budesonide as to produce an incidence of systemic side-effects and adrenal suppression similar to that caused by conventional steroids.

Aminosalicylates (Table 1)
Suphasalazine is firmly established in the management of active colitis (both UC[4] and CD[5]), and in the maintenance of remission in UC[4]; the same applies to its sulphapyridine (and therefore relatively side-effect) free derivatives, whether in bacterially-liberated ( olsalazine, balsalazide), enteric-coated pH released [Asacol, Claversal, Salofalk (mesalazine e. c. )] or slow-release [Pentasa (mesalazine s. r.)] formulations.

Like corticosteroids, aminosalicylates have a wide variety of anti-inflammatory effects, although which of these explain their efficacy in IBD is not known. These actions include inhibition of leucocyte migration and cytotoxicity; reduced activation of NFkB; inhibition of the synthesis of lipid mediators (leucotrienes, thromboxanes, prostaglandins, PAF) and of interleukin-1; reduction of prostaglandin degradation; antioxidant

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### Table 1: New formulations and applications of existing therapies for IBD

| Treatment          | Agent                                      | References |
|--------------------|--------------------------------------------|------------|
| Budesonide         | Non-pathogenic *E. coli*                   | 41-42      |
| Aminosalicylates   | Short chain fatty acids*                   | 43-46      |
|                     | Apheresis, anti-CD4 antibodies, bone marrow transplant | 47-50      |
|                     | Adhesion molecule antibodies or antisense oligonucleotide | 51         |
|                     | NFB antisense oligonucleotide              | 10         |
|                     | Anti-TNF antibodies*, IL-1                 | 52-55      |
|                     | Antagonist inflammatory cytokines          |            |
|                     | cytokines                                 |            |
|                     | IL-10*, interferon alpha or beta          | 56         |
|                     | TNF antibodies*, IL-1                     |            |
|                     | Synthesis inhibitors and receptor antagonists of leucotrienes, COX2 inhibition | 11,57-60,67 |
|                     | 11,57-60,67                               |            |
|                     | 11,57-60,67                               |            |
|                     | Antioxidants                              | 12,61      |
|                     | Inducible NOS inhibition                   | 62         |
|                     | Fish oil (EPA)                            | 63-66      |
|                     | Heparin*                                  | 67-68      |
|                     | Local anaesthetics*                       | 69-71      |
|                     | Nicotine (UC)*, stopping smoking (CD)*     | 72-75      |

*Denotes current or imminent option
effects; TNF antagonism; and in epithelial cells, induction of heat shock proteins and inhibition of apoptosis and MHC Class II expression.

In active ileo-caecal CD, recent interest has focussed on the use of mesalazine slow-release (Pentasa), a preparation which delivers high concentrations of 5-aminosalicylic acid to the small bowel as well as colon. In one study, this preparation, given in high dose (4 g/day) for 16 weeks, resulted in a remission rate of 43% in patients with active ileo-caecal CD, while lower doses (1 g and 2 g) were no more effective than placebo (remission rates 18% - 24%)\(^{19}\).

While several individual studies in the last 10 years have suggested that aminosalicylates may also have a role in maintaining remission in inactive CD, a recent meta-analysis has shown this effect to be minimal, with a reduction in relative risk of symptomatic relapse at 1 year in patients on mesalazine as opposed to placebo of only 6%, and in post-operative patients of 13%.\(^{23}\) Cost-benefit issues in relation to longterm use of these relatively expensive drugs in inactive CD clearly need resolution.

Aminosalicylates have a dose-related therapeutic role in moderately active (although not acute severe) UC and, particularly, in patients with inactive disease, in whom they reduce annual relapse rates to about 25% compared with 75% in placebo-treated patients. In patients with left-sided active UC, clinical trials support the theoretical proposal that drugs delivering 5 aminosalicylate (5-ASA) primarily to the colon (salsalazine, balsalazide) may be more effective than those from which 5-ASA is released more proximally, e.g. Asacol\(^{21,22}\).

**Immunomodulatory drugs (Table 1)**

**Azathioprine and 6-mercaptopurine** The benefits of azathioprine and its metabolite, 6-mercaptopurine, as second-line agents in the management of chronic IBD are now widely accepted\(^{23}\). These agents inhibit purine nucleotide biosynthesis and appear thereby to modify T lymphocyte function.

Azathioprine is useful in maintaining remission of both UC\(^{24}\) (in patients failing to respond adequately to aminosalicylates) and CD\(^{25}\), and as a steroid-sparing drug in the minority of patients with either disease who relapse repeatedly on steroid withdrawal\(^{23}\); it may also play special roles in accelerating remission and healing ileal lesions when given in combination with prednisone in active CD\(^{26,27}\) and in Crohn’s patients with perianal disease\(^{23}\).

Apart from their side-effects (nausea, vomiting, headache, joint pains, rash, fever, and, more seriously, bone marrow depression, acute pancreatitis, chronic hepatitis and possible malignancy in longterm users), the main disadvantages of a zathioprine and 6-mercaptopurine are that they take up to 4 months to act when given orally. Trials to assess the possibility of accelerating the clinical response in active CD using intravenous azathioprine are in progress\(^ {28}\). If results prove successful, use of this route of administration will demand prior assay of red blood cell concentration of 6-thiopurine methyltransferase (6-TPMT), homozygous deficiency of which can be fatal as a result of failure of inactivation of 6-mercaptopurine.

A French report showed that, in patients with inactive CD, the risk of relapse after 4 years of successful treatment with azathioprine (or 6-mercaptopurine) was similar whether the immunosuppressive agent was continued or stopped; The authors suggested that, in view of the potential toxicity of long-term use of azathioprine, its withdrawal should be considered in patients who had remained in remission after 4 years’ treatment\(^ {29}\).

**Cyclosporine** Cyclosporine inhibits helper-and cytotoxic T-lymphocyte function and proliferation, mainly through inhibition of interleukin-2 gene transcription. It also reduces interferon-gamma, interleukin-3 and interleukin-4 production.

Interest in the use of intravenous cyclosporine in active CD was stimulated by Brynskov’s provocative report in 1989\(^ {30}\), but subsequent trials have cast a dampener on the use of this agent, at least in low dose, in Crohn’s.

In contrast, in a single small controlled study\(^ {31}\), the results of which have been largely confirmed by subsequent experience elsewhere, intravenous (4 mg/kg·day) followed by oral (5 - 8 mg·kg·day) cyclosporin, given in addition to continuing corticosteroids, averted colectomy in the acute phase in about 80% of patients with acute severe UC who had failed to respond to 5-7 days of intravenous steroids.

Enthusiasm for this approach, however, needs to be tempered both by the frequency of relapse necessitating colectomy (up to 50%) that follows withdrawal of cyclosporine, and by its serious side-effects. Acutely, these include opportunistic infections, particularly pneumocystis carinii pneumonia; renal impairment including a 20% reduction in glomerular filtration rate in most patients, and an often irreversible interstitial nephritis in up to 25% patients; hypertension, hepatotoxicity, epileptic fits, hyperkalaemia, hyperuricaemia, hypertrichosis and paraesthesiae. Longterm oral use may predispose to lymphoma. The side-effects of cyclosporine necessitate frequent
monitoring of cyclosporine blood levels and serum biochemistry in treated patients. At present, use of cyclosporine in acute severe UC should probably be restricted to clinical trials and specialist centres familiar with its use. Further studies are needed to define which patients should be given the drug intravenously, and what continuing oral therapy, for example cyclosporin, azathioprine or 6-mercaptopurine, they should be prescribed thereafter. It is possible, however, that intravenous cyclosporine, perhaps given with prophylactic trimethoprim/sulphamethoxazole, may turn out to be very useful, in the minority of patients with steroid-refractory acute severe UC, for buying time for improving their nutrition prior to, and/or preparing them psychologically for surgery.

**Methotrexate** Methotrexate is an immunosuppressive agent widely used in difficult rheumatoid arthritis and psoriasis. A North American group reported that this drug, given once a week as a 25 mg intramuscular injection, was superior to placebo in improving symptoms (remission rates at 16 weeks 40% and 20%, respectively) and reducing requirements for prednisone in steroid-dependent CD. In chronic steroid-dependent UC, in contrast, a lower dose of methotrexate (12.5 mg), given orally once weekly, was no more effective than placebo in the induction of remission or its maintenance over a 9 month period. Whether use of methotrexate in IBD becomes widespread will depend on the success of rival agents with fewer side-effects.

**Mycophenolate mofetil** Very recently, a preliminary study suggested that mycophenolate mofetil, a T-cell inhibitor used increasingly in the prevention of transplant rejection, may be of value in refractory Crohn’s disease. This drug appears to be relatively non-toxic, although expensive, and is currently undergoing controlled trial in CD.

**Antibiotics (Table 1)**

- **Metronidazole** Metronidazole acts not only against a range of anaerobes and protozoa, but also has immunomodulatory effects. Controlled trials have shown that oral metronidazole (800 mg/day) has moderate benefit in ileocolonic CD, and in preventing recurrence after ileal resection, while open studies indicate that it may also be effective in perianal CD. Treatment needs to be given for up to 3 months, and may be complicated by nausea, vomiting and unpleasant reactions when combined with alcohol; more importantly, it may induce a peripheral neuropathy not always reversible on its discontinuation.

**Other antibiotics** Anecdotal reports and uncontrolled trials have suggested possible roles for clarithromycin and ciprofloxacin in CD, the latter particularly for perianal disease, and for trimethoprim/sulphamethoxazole in acute severe UC. Tobramycin given orally in addition to steroids and sulphasalazine improved remission rate in active UC, and some gastroenterologists use this or another broad-spectrum antibiotic as prophylaxis against bacteraemia and endotoxic shock in severely ill patients with acute severe UC.

**Dietary Therapy (Table 1)**

There is no specific dietary therapy for patients with UC, although a few (<5%) may improve with avoidance of cow’s milk, and some with proctitis and proximal constipation may benefit from fibre supplementation. Patients with stricturing small bowel CD should avoid high residue foods (e.g. citrus fruit segments, nuts, uncooked vegetables) which might cause bolus obstruction. All patients with IBD, particularly if it is active or extensive, are at risk of nutritional deficiencies which need replacement as necessary.

Over the last 20 years, it has become clear that in children with CD, as well as in adults with extensive small bowel disease and in those who respond poorly to, or prefer to avoid corticosteroids, an alternative therapy is a liquid formula diet. This can either be elemental (aminoacid-based), protein hydrolysate (peptide-containing) or polymeric (containing whole protein and not therefore hypoallergenic), and is given for 4-6 weeks as the sole nutritional source. This approach is probably as effective as corticosteroid therapy in the short-term, about 60% patients achieving remission. Unfortunately, after the resumption of a normal diet, many patients relapse (50% at 6 months): whether this can be prevented by selective and gradual reintroduction of particular foods to which individual patients are not intolerant, or by the intermittent use of further enteral feeding for short periods, remains to be proven.

The success of enteral nutrition as a primary treatment for CD is also limited by its cost, the unpleasant taste of some of the available preparations, the need often to give the feed by nasogastric tube, and the poor compliance of many patients in adhering to it. Such therapy does, nevertheless, offer a valuable alternative in the well-motivated minority of patients for whom it is appropriate.

**New Therapies Aimed at Specific Pathophysiological Targets (Table 2)**

Elucidation of the pathogenesis of IBD has led to
the evaluation in experimental animal models, and to a lesser extent in the human disease, of several different therapeutic approaches aimed at specific pathophysiological targets (Table 2). Where substantial data in humans, will now be briefly discussed.

**Non-pathogenic escherichia coli**

There is some evidence that patients with UC have increased proportions of adhesive and enterohaemorrhagic E coli in their large bowel. Two preliminary reports suggest that oral administration of capsules containing non-pathogenic E coli may have a role in maintaining remission in patients with inactive UC\[41,42\], but further work is required to confirm the efficacy of this or other (e.g., lactobacillus) probiotic approaches.

**Short chain fatty acids (SCFA)**

Normal colonic epithelial cells depend for their energy metabolism on a luminal supply of SCFA, derived from bacterial flora. In UC, colonocytes inadequately utilise SCFA; low luminal SCFA levels in UC exacerbate this metabolic defect\[43\]. Efforts to remedy the defect by treatment of patients with distal UC with enemas containing SCFA, principally butyrate, have unfortunately not proved uniformly successful\[44-46\]; furthermore, the appeal of this very safe therapy is restricted by the unpleasant smell of the enemas.

**Modifying leucocyte numbers and function**

Depleting leucocyte numbers, by use of leucocyte apheresis, antiCD4 antibodies or bone marrow transplantation, has been shown in uncontrolled reports to suppress activity of CD\[47-49\]; a similar effect is seen in AIDS when the CD4 count falls\[50\]. Furthermore, trials are in progress to assess the clinical efficacy in IBD of inhibiting leucocyte migration into the gut mucosa using antibodies or antisense oligonucleotides to adhesion molecules such as ICAM-1\[51\]. As with other major immunomodulatory therapies, it is not yet clear whether the benefits of such approaches will outweigh their cost, complexity and, particularly, toxicity in relation to the risks of infection and malignancy.

**Modulation of cytokine activity**

Recognition of altered cytokine expression in IBD has prompted therapeutic trials using interleukin-1 receptor antagonist, interferon-alpha and gamma, anti-TNF-alpha antibody and interleukin-10 (IL-10): of these, the last two are the most promising.

**Anti-TNF-alpha antibody**

Controlled trials have shown that intravenous infusions of either mouse/human chimeric (cA2) or 95% humanised (CDP571) anti-TNF-alpha antibody induced remission in active refractory CD\[52,53\] and healed Crohn’s fistulae\[54\]; uncontrolled studies suggest efficacy in UC too\[55\]. The published results are impressive, mucosal lesions healing completely in many instances. However, the relative merits of cA2 and CDP571 require clarification in relation to their efficacy, safety and cost. Reassurance is needed that repeated usage will not lead to adverse effects as a result of host antibody induction, or of immunosuppression with consequent opportunistic infection or malignancy. Definition of which patients are most likely to benefit from this very specialist treatment is also needed: this may relate not only to their disease phenotype (e.g., fistulating disease), but also their genotype (e.g., TNF microsatellite subtype).

**Interleukin-10** IL-10 is an anti-inflammatory and immunosuppressive cytokine. A recent placebo-controlled trial of recombinant human IL-10 gave promising results in steroid-refractory CD\[56\], and further reports are imminent.

**Antisense oligonucleotide to NFkB**. The upregulation of NFkB in IBD tissue may play a central role in its pathogenesis as a result of stimulation of the synthesis of proinflammatory cytokines such as TNF, IL-1 and IL-6\[10\]. It remains to be seen whether trials of antisense oligonucleotides to NFkB will prove as effective and safe in human IBD as they appear to be in experimental colitis in mice\[10\].

**Modifying the effects of lipid mediators**

Reducing synthesis of proinflammatory prostaglandins with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has an adverse rather than beneficial effect in IBD, perhaps because of the concomitant suppression of cytoprotective prostaglandins\[11\]. The efficacy and safety of selective cyclooxygenase-2 (COX2) inhibitors have not yet been formally assessed in IBD. Trials with inhibitors of the synthesis of the extremely potent inflammatory mediator, leucotriene B4, in UC have shown at best a very modest benefit\[57,58\]. Ridogrel, a dual thromboxane synthesis inhibitor and receptor antagonist\[59\], has been shown to induce remission in over 40% patients with moderately active UC\[60\], and is under trial in active Crohn’s. Antagonists to platelet activating factor (PAF) have been ineffective in active UC.

**Antioxidants**

While enhanced mucosal production of reactive
oxygen metabolites is well established, published trials of antioxidant therapy in human IBD are limited to one open study of patients with steroid-resistant CD who appeared to benefit from intramuscular injections of superoxide dismutase. Despite the lack of controlled data available, many patients with IBD in the West use over the counter antioxidant drugs in an effort to ameliorate their disease.

Although increased mucosal generation of nitric oxide may contribute to the pathogenesis of IBD, there is no data yet to support the hypothesis that selective inhibition of inducible nitric oxide synthase may be beneficial.

**Fish oil (eicosapentaenoic acid, EPA)**

EPA, the active ingredient of fish oil capsules, decreases synthesis of leucotriene B4, thromboxane A2, prostaglandin E2, platelet activating factor and interleukin-1. Although these actions should make it a useful anti-inflammatory agent, trials in UC have shown that high doses produce only modest clinical improvement: in addition, the strong fishy odour on the breath associated with consumption of EPA preparations is likely to inhibit their widespread use.

More recently, an enteric-coated fish oil preparation, which is better tolerated than standard formulations, although is not yet commercially available, has been reported to reduce substantially the relapse rate in patients with inactive CD (relapse rate at 1 year 28% on fish oil, 69% on placebo). This exciting result, if confirmed by other groups, could become a very useful and, probably, safe form of maintenance therapy in CD: the apparently beneficial cardiovascular effects of EPA would contribute to its popularity with patients.

**Modulation of procoagulant state**

Active IBD is characterised by a procoagulant diathesis which may contribute not only to the increased risk of systemic thromboembolism characteristic of the disease, but also to the intramucosal inflammatory process. Several recent pilot studies suggest that intravenous heparin may have a beneficial effect on disease activity in both UC and CD, and controlled studies are in progress. Mechanisms of action of heparin in IBD are likely to include interference with leucocyte-endothelial cell adhesion and of platelet activation as well as its anticoagulant effects.

**Modulation of enteric nerve function**

Neuronal hyperplasia, hypertrophy and degeneration, together with abnormalities of neurotransmitter content, have been described in the gut mucosa of patients with IBD. In open studies, Bjorck et al have reported clinical and sigmoidoscopic improvement in 90% of UC patients treated with lidocaine enemas for up to 12 weeks; similar uncontrolled results using ropivacaine gel rectally have been published more recently. This approach needs to be validated by controlled trials; whether any beneficial effect of lidocaine or other local anaesthetics is due to modulation of enteric nerve function or to inhibition of production by mucosal leucocytes of inflammatory mediators is unclear.

**Smoking: Nicotine**

Smoking is rare in patients with UC and anecdotal reports have suggested that some individuals can control their disease by judicious indulgence in this otherwise undesirable habit. Two controlled studies have confirmed that nicotine patches can induce remission in active UC, although, surprisingly, cannot maintain it. Studies are in progress to assess the efficacy of alternative formulations of nicotine (for example in oral pH-release capsules or enemas) which, by allowing first-pass hepatic metabolism of nicotine will avert the systemic side effects produced by skin patches, and allow the use of higher doses. The mechanism of the therapeutic effect of nicotine in UC, some of the pharmacological effects of which appear to be pro-inflammatory, is unknown: possibilities include increased colonic mucus secretion, alterations of cell-mediated immunity, and reductions in gut permeability, prostaglandin E2 production and rectal mucosal blood flow.

Smoking has an adverse effect on the natural history of CD, including the reoperation rate: patients with CD who smoke should be advised to stop.

**TRADITIONAL MEDICINE**

In the West, a substantial minority of patients with IBD, dissatisfied with conventional pharmacological treatment, resort to alternative therapies including herbal medications such as aloe vera, relaxation, aromatherapy, acupuncture and homeopathy. Unfortunately, however, there appear to be very few reports of the efficacy of such therapy, at least in the English language literature. Controlled studies of traditional medical treatment of IBD are urgently needed.

**CONCLUSIONS**

There is still no entirely effective, safe, cheap treatment for the suppression of IBD, let alone its cure.

Amongst the conventional alternatives, the
major recent advances are the development of oral corticosteroids, such as budesonide, with few systemic side-effects, and of new aminosalicylates, such as mesalazine slow-release for CD and balsalazine for UC. The side-effects of existing immunomodulatory agents, with the possible exception of azathioprine, make them unlikely to achieve a major role in patients with uncomplicated disease. Liquid formula diets are effective and safe in patients with active small bowel CD, but the value of traditional medical treatment in IBD is as yet unproven.

Of the drugs designed to rectify specific pathophysiological abnormalities in IBD, short chain fatty acids and lidocaine enemas are occasionally useful in patients with refractory distal UC. Injections of anti-TNF antibody and interleukin-10 may prove to be a major step forward in patients with difficult IBD, but their safety in the long- as well as short-term requires confirmation. Other “designer-drugs” have proved disappointing to date, perhaps because their effects on the complex inflammatory response are, unlike those of corticosteroids and aminosalicylates, too accurately focussed on specific, but redundant mediator pathways. We still need to learn what makes the inflammatory response in the mucosa of patients with UC and Crohn’s persist chronically: it is possible that identification of this key abnormality will, in the absence of the discovery of a reversible primary cause, offer the best hope of developing an effective new therapy for patients with IBD.

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