Novel treatments in inflammatory bowel disease

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Recent advances in inflammatory bowel disease therapeutics have led to improved formulations of existing treatments and new indications for established drugs. Truly novel therapies based on recent understanding of pathogenesis are also being developed. These new treatments and their likely impact on the management of inflammatory bowel disease in the future are discussed.

The term inflammatory bowel disease (IBD) encompasses two diseases namely ulcerative colitis (UC) and Crohn's disease. Although aetiology remains obscure, pathogenesis is thought to be multifactorial, based on an excessive and inappropriate immune response to as yet unidentified luminal antigen(s). The extent of this abnormal immune response is likely to be both genetically and environmentally influenced (*Figure 1*). A number of inflammatory mediators are elevated in IBD tissue (*Figure 2*), but it is unclear at present whether this is a primary or secondary event or to what extent there is an imbalance of pro-inflammatory and anti-inflammatory molecules (Fiocchi, 1998).

The rationale for the use of anti-inflammatory and immunosuppressive agents in the treatment of IBD is based on these observations. Drug treatment on a clinical level is divided into the treatment of an acute exacerbation and the maintenance of remission once this is attained.

This article will review recent modifications of established therapies for IBD, and will also examine truly 'novel' therapies undergoing current clinical evaluation, including genetically engineered biological therapies which may have a significant impact in the future.

OLD DRUGS WITH NOVEL MODIFICATIONS AND USES

Aminosalicylates

Aminosalicylates have long been used in UC and remain the treatment of choice for maintenance of remission. The recognition that 5-ASA is the active moiety of sulphasalazine has lead to new formulations of the 5-ASA molecule to deliver it to distal small bowel and colon. This includes replacing sulphapyridine, which is responsible for many of the side-effects, with another carrier which is split by bacterial azo-reductases in the intestine releasing the active compound (olsalazine, ipsalazine, balsalazine).

An alternative method of delivery is to coat 5-ASA with a slow-release membrane to prevent gastric breakdown (Pentasa, Ferring, Copenhagen; Asacol, Smith Klein and French, Crawley). Of these, balsalzine (marketed as Colazide, Astra, Gothenberg) is the most recently launched and has been reported to be more effective and better tolerated than delayed release mesalazine in acute relapse of UC (Green et al, 1998), although it remains to be seen whether it is better than other 5-ASA formulations for maintenance therapy.

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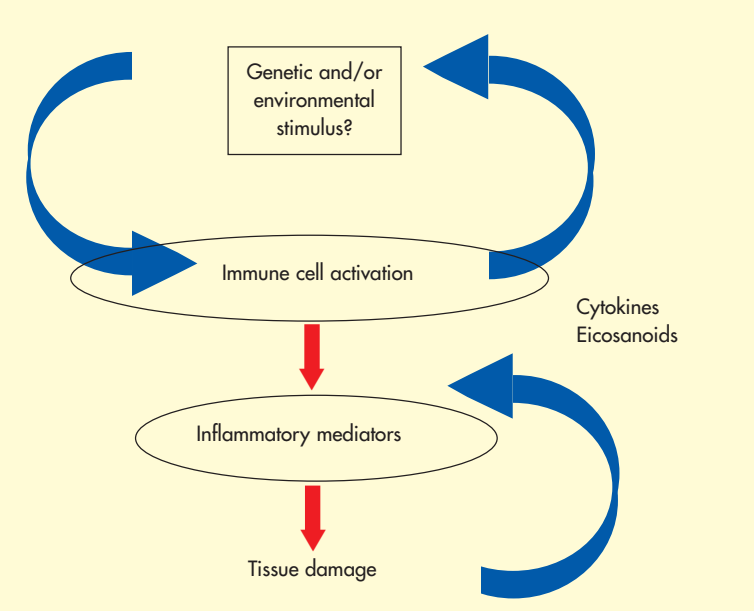

Figure 1. Events leading to chronic inflammation in Crohn's disease and ulcerative colitis.

Corticosteroids

Oral corticosteroids are used primarily to induce remission in acute IBD. Recent developments have focused on enhancing potency while limiting systemic effects. In this regard, budesonide has emerged with the most potential in IBD. This highly potent topically active corticosteroid can be delivered locally as an enema, or orally in a delayed release capsule (Entocort, Astra, Gothenberg). Once absorbed, it is quickly degraded by erythrocytes and the liver, limiting the availability of steroid to cause systemic side-effects.

In acute UC, oral budesonide has been demonstrated to be as good as prednisolone in inducing overall remission although it was less effective in healing distal disease (Lofberg et al, 1996). In Crohn's disease budesonide has also been investigated for the treatment of both active disease and in the maintenance of remission, where it has been proven to be almost as good as prednisolone and significantly better than placebo (Lofberg, 1995). Studies with this formulation of budesonide in IBD thus far have demonstrated that it does not affect the hypothalamic–pituitary–adrenal axis in the short term, but long-term follow-up studies to investigate potential problems such as osteoporosis are needed.

Azathioprine

Azathioprine is now widely used for maintaining remission in difficult Crohn's disease and UC. The most recent innovation in the use of azathioprine has been to administer a high intravenous loading dose to decrease the time to response (Sandborn et al, 1995). Twelve patients with Crohn's disease (6 with fistulae and 6 with inflammatory disease) received a continuous intravenous infusion of azathioprine 50 mg/h for 36 hours followed by oral therapy. Over half the fistulae had closed and two thirds of those with inflammatory disease had improved within 4 weeks with no significant adverse events seen. It is not known whether a similar strategy would be successful in acute UC.

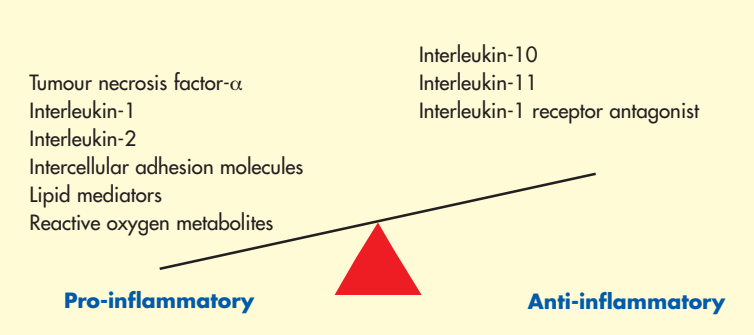

Figure 2. Imbalance of pro-inflammatory and anti-inflammatory mediators in inflammatory bowel disease.

Cyclosporin

Cyclosporin has been investigated in clinical trials for both Crohn's disease and UC. The major advantage of cyclosporin is its speed of action, which is measured in days rather than weeks. In Crohn's disease, controlled trials have not demonstrated a significant benefit in either acute disease or for maintenance of remission. (Sandborn, 1995). However, in acute UC results have been more encouraging although there are much fewer controlled data.

In a placebo controlled trial of cyclosporin in acute steroid-resistant colitis involving 20 patients, 9 out of 11 responded to cyclosporin in the short term compared to 0 of 9 receiving placebo (Lichtiger et al, 1994). However, approximately half of those initially responding to cyclosporin will require colectomy in the long term (Stack et al, 1998). Presently, there are few data on the effectiveness of using cyclosporin alone for acute UC or whether the addition of another immunosuppressant after stopping cyclosporin is necessary for maintenance of remission, although this is commonly done in practice.

Methotrexate

Methotrexate suppresses T-cell function by decreasing folate-dependent enzyme activity in lymphocytes and has recently been investigated in Crohn's disease. In a randomized study of 141 patients with active Crohn's disease who were unresponsive to 3 months of treatment with corticosteroids, methotrexate 25 mg intramuscularly weekly induced remission in 39% of treated patients compared with 19% given placebo injections (Feagan et al, 1995). However, there was a higher dropout rate in the methotrexate group because of adverse effects. It may also be useful in refractory UC where open studies have suggested benefit but its place in the long-term management of IBD is yet to be determined.

Other treatments

Following anecdotal evidence of improvement in colitis with heparin, an open study suggested that it might be of genuine use in UC (Gaffney et al, 1993). This may at first appear to be counter-intuitive, as bloody diarrhoea is a cardinal symptom of acute UC. However, heparin also has a wide range of anti-inflammatory activities, mainly by binding pro-

inflammatory mediators. Further controlled data will be required before the acceptance of heparin for acute UC in practice.

Epidemiological studies have shown that smoking is positively associated with Crohn's disease but negatively associated with UC. Transdermal nicotine has been evaluated with mixed results in the treatment of acute UC and for the maintenance of remission. In mild to moderately active UC, a cumulative risk difference of +19% favouring treatment has been reported (Pullan et al, 1994), although a significant number of adverse effects were also observed.

Future applications for this drug may be in subsets of patients who have stopped smoking and subsequently suffered disease relapse. Other treatments which have recently been used with variable success in IBD include ciprofloxacin, butyrate enemas and topically applied lignocaine for distal proctitis but none have gained universal acceptance as of yet.

NOVEL DRUGS WITH SPECIFIC TARGETS

It has recently emerged that a number of pro-inflammatory and anti-inflammatory mediators are found in raised concentration both in Crohn's disease and UC (*Figure 2*). This discovery has led to the development of therapies targeted at key sites for promoting or interfering with processes involved in the regulation of the inflammatory cascade (*Tables 1* and *2*).

Anti-tumour necrosis factor-α therapy

Tumour necrosis factor-α (TNFα) as a future target has probably received the most recent attention in IBD. TNFα causes immune cell activation and other inflammatory mediator release in IBD. TNFα can be neutralized at a number of points along its metabolism and success with monoclonal antibodies against TNFα has been reported in IBD (*Figure 3*). These antibodies are raised in mice against human TNFα and these are genetically modified to make them less immunogenic.

There are two anti-TNFα antibodies currently undergoing evaluation in Crohn's disease. Infliximab (Centacor, Leiden, The Netherlands) is a chimeric mouse/human antibody based on a gamma-1 heavy chain which activates complement in addition to neutralizing soluble and cell bound TNFα. In a placebo controlled study of a single infusion of infliximab in steroid-resistant Crohn's disease, 33% achieved remission, and 65% had a clinical response compared with 17% given placebo (Targan et al, 1997).

Success with treating fistulous Crohn's disease has also been reported for infliximab, which has been recently licensed by the Food and Drug Administration in the USA for use in severe Crohn's disease.

CDP571 (Celltech, Slough, Berks) is another anti-TNFα antibody which is also currently been investigated in Crohn's disease. It differs from infliximab in that it is based on a gamma-4 heavy chain which will not activate complement, and it contains less mouse material in its complementarity-determining region. In a recent trial, 30 patients with active Crohn's disease were treated with a single 5 mg/kg infusion of

TABLE 1.
Specific targets for therapeutic activity in inflammatory bowel disease

T cells
Cytokines
Adhesion molecules
Lipid-derived mediators
Reactive oxygen metabolites
Gut flora

TABLE 2.
Genetically engineered therapies currently being evaluated in inflammatory bowel disease

Tumour necrosis factor-α antibodies	CDP571
	Infliximab
Interleukin-10	
Interleukin-11	
ICAM-Antisense	ISIS 12302

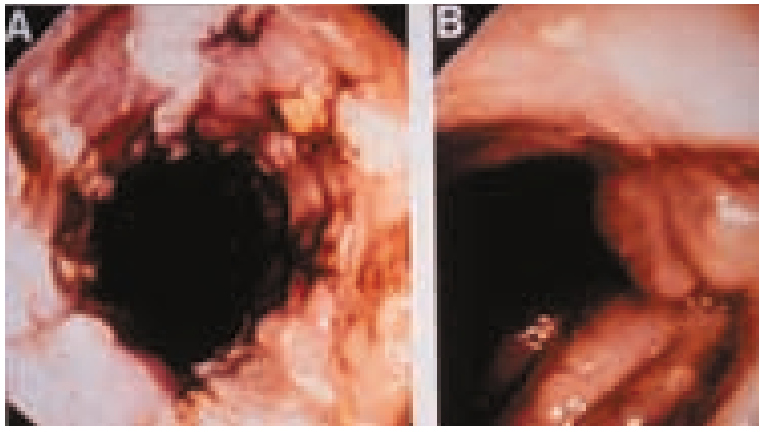

Figure 3. Healing of colonic ulceration in Crohn's disease after a single infusion of tumour necrosis factor-α antibody. From van Dullemen et al (1995).

CDP571 or placebo. After 2 weeks, disease activity had reduced significantly in 20 patients treated with CDP571 with little change in 10 patients treated with albumin as control (Stack et al, 1997).

Although no serious short-term adverse events were seen, approximately 9% of patients developed anti-double stranded DNA and 1 lymphoma has been reported in a patient with Crohn's disease treated with infliximab (who was also receiving azathioprine). Long-term follow-up of these patients is therefore necessary. As the initial results for the use of these antibodies in the treatment of Crohn's disease are promising, both are undergoing further assessment in ongoing clinical trials.

Interleukins

Interleukin-1 (IL-1) is a pro-inflammatory cytokine, produced mainly by macrophages and monocytes, which is released in large quantities in IBD. This is accompanied by synthesis of an inhibitory molecule, IL-1 receptor antagonist (IL-1 RA) which competes with IL-1. Inhibiting the synthesis of IL-1 or upregulating IL-1 RA has been successful in animal models of IBD although no human data are currently available.

Regulatory cytokines also play an important role in limiting the inflammatory response (*Figure 1*). SCH 52000 (recombinant IL-10, Shering-Plough, New Jersey, USA) was administered in 46 patients with active Crohn's disease. Remission was seen in 50% of patients treated compared with 23% given placebo (van Deventer et al, 1997). IL-11 has also shown promise in Crohn's disease and follow-up studies are underway for both of these anti-inflammatory cytokines to confirm early results.

Antagonists to lipid-derived mediators

UC is accompanied by enhanced secretion of lipid-derived mediators including leucotriene B4 (LTB4), platelet-activating factor (PAF) and thromboxane. Antagonists of these products have been effective in reducing inflammation in animal models of IBD. However, specifically inhibiting lipid mediators, including LTB4 and PAF, has been ineffective in acute UC (Stack and Hawkey, 1997).

An alternative method of altering the eicosanoid profile is by administration of fish oil which increases the concentration of less damaging eicosanoids in tissues. One problem with fish oil therapy up to now is that it is often poorly tolerated by patients because of its smell and taste. However, using an enteric coated formulation, fish oil gave a remission rate at 1 year of 59% compared to 26% of patients treated with placebo in a maintenance study in Crohn's disease (Belluzzi et al, 1996). There is little evidence to suggest fish oil is of any benefit in UC.

Adhesion molecules and anti-sense therapy

Recruitment of leukocytes into the inflammatory focus is important for amplifying the immune response in IBD. Adhesion molecules such as selectins and integrins are important for leukocyte trafficking from the blood to the site of inflammation. It is now possible to block the synthesis of adhesion molecules by specifically targeting the nuclear translation of messenger RNA.

ISIS 2302 is an anti-sense molecule which binds to the nuclear site where messenger RNA for intercellular adhesion molecule-1 is synthesized and blocks its production. In patients with active Crohn's disease, three weekly infusions with ISIS 2302 for 4 weeks induced remission in 7 out of 15 (47%) patients treated in comparison with 1 out of 5 given placebo (Yacyshyn et al, 1998). However, ISIS 2302 has a very short half-life as it is easily degradable and has to be given frequently to be effective. Further studies in Crohn's disease are ongoing at present.

Probiotic and antibiotic agents

Altered bacterial populations in the colon may be responsible for relapse of IBD. This has raised the possibility of administering 'probiotic' bacterial flora as a form of microbial interference treatment in order to disrupt the activity of the original bacterial insult. Bacterial preparations consisting of *Lactobacilli* and *Bifidobacter* have recently been shown to be effective in ileoanal pouchitis (Gionchetti et al, 1998). Early indications also show that an oral preparation of a non-pathogenic *Escherichia coli* compares favourably with standard drug therapy, producing similar relapse rates and almost identical relapse-free intervals (Kruis et al, 1997). There is likely to be considerable interest in altering bacterial populations as a therapeutic target for IBD in the future.

OTHER NOVEL TARGETS

Reactive oxygen metabolites (ROM) including hydrogen peroxide, superoxide and hydroxyl radicals play an important role in tissue damage. ROM scavengers such as superoxide dismutase have been used with variable efficacy in IBD but none have appeared in practice at this time. Nitric oxide (NO) is another ROM which is cur-

rently being evaluated in bowel inflammation. Although excess NO is associated with active disease, drugs which non-specifically inhibit the synthesis of NO appear to have little effect on inflammation in animals. However, drugs which only inhibit excess NO synthesis are being developed and it remains to be seen whether these will be effective in the treatment of IBD in the future.

CONCLUSIONS

Although the aetiology of IBD is still elusive, insights into the pathogenesis have resulted in identification of many potential target sites for new therapies along the inflammatory cascade. The search for novel and effective therapeutic agents is continuing. Many of the newer biological therapies are administered parenterally and are likely to be expensive. Once more key processes are understood, further modification of present therapies along with more novel treatments based on traditional carbon-based drugs should result in more effective and safer treatments in the future. HM

Figure 3 *is reproduced by kind permission of Saunders, USA.*

Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M (1996) Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* **334:** 1557–60

Feagan BG, Rochon J, Fedorak RN et al (1995) Methotrexate for the treatment of Crohn's disease. *N Engl J Med* **332**: 292–7

Fiocchi C (1998) Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology* **115:** 182–205

Gaffney PR, Doyle CT, Hogan J, Gaffney A (1993) Paradoxical response to heparin in 10 patients with ulcerative colitis. *Am J Gastroenterol* **90**: 220–3

Gionchetti P, Rizzello F, Venturi A et al (1998) Maintenance treatment of chronic pouchitis: a randomised placebo controlled, double-blind trial with a new probiotic preparation. *Gastroenterology* **114:** A1959

Green JRB, Lobo AJ, Holdsworth CD et al (1998) Balsalazide is more effective and better tolerated than mesalazine in the treatment of acute ulcerative colitis. *Gastroenterology* **114:** 15–22

Kruis W, Schuetz E, Fric P, Fixa B, Judmaier G, Stolte M (1997) Double blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* **11:** 853–6

Lichtiger S, Present DH, Kornbluth A et al (1994) Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* **330:** 1841–51

Lofberg R (1995) New steroids for inflammatory bowel disease. *Inflamm Bowel Disease* **1:** 135–41

Lofberg R, Danielsson A, Suhr O et al (1996) Oral budesonide *vs* prednisolone in patients with active extensive and left-sided colitis. *Gastroenterology* **110:** 1713–8

Pullan RD, Rhodes J, Ganesh S et al (1994) Transdermal nicotine for ulcerative colitis. *N Engl J Med* **330:** 811–5

Sandborn WJ (1995) A critical review of cyclosporine therapy in inflammatory bowel disease. *Inflamm Bowel Disease* **1:** 48–63

Sandborn W, Van Os E, Zins B, Tremaine W, Mays D, Lipsky J (1995) An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. *Gastroenterology* **109:** 1808–17

Stack WA, Hawkey CJ (1997) Mediator directed therapy in gastrointestinal diseases. *Eur J Gastroenterol Hepatol* **9:** 1056–61

Stack WA, Mann SD, Roy AJ et al (1997) Randomised control trial of CDP571 antibody to tumour necrosis factor alpha in Crohn's disease. *Lancet* **349:** 521–4

Stack WA, Long RG, Hawkey CJ (1998) Short-term and long-term outcome of patients treated with cyclosporin for severe acute ulcerative colitis. *Aliment Pharmacol Ther* **12:** 973–8

Targan SR, Hanauer S, van Deventer SJH, et al (1997) A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor-alpha for Crohn's disease. *N Engl J Med* **337:** 1029–34

van Deventer SJH, Elson CO, Fedorak RN (1997) Multiple doses of interleukin-10 in steroid-refractory Crohn's disease. *Gastroenterology* **113:** 383–9

van Dullemen H, van Deventer S, Hommes D, Hannie A, Jansen J, Tytgat G, Woody J (1995) Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* **109**: 129–35

Yacyshyn BR, Bowen-Yacyshyn MB, Jewell L, Tami JA, Bennett CF, Kisner DL, Shanahan WR (1998) A placebo-controlled trial of ICAM-antisense oligonucleotide in the treatment of Crohn's disease. *Gastroenterology* **114:** 1133–42

KEY POINTS

- Despite increasing insight into the pathogenesis of inflammatory bowel disease, no medical cure is available.
- Recent modifications of aminosalicylates and corticosteroids have probably made them safer to use in inflammatory bowel disease.
- Novel genetically engineered drugs targeting specific sites in the inflammatory cascade are likely to have an impact in the near future.
- Of these novel treatments, tumour necrosis factor-α antibodies will shortly be available for Crohn's disease.
- Other genetically engineered biologic therapies including anti-inflammatory cytokines (interleukin-10, interleukin-11) and anti-sense therapies are currently being evaluated in inflammatory bowel disease.
- Once key processes in the inflammatory cascade are identified it may be possible to return to orally delivered carbon-based drugs.