



Advances in Management of Inflammatory Bowel Disease: The Biological Therapies Era

Subrata Ghosh*, Rakesh Chaudhary**

*Chair in Gastroenterology, **Clinical Research Fellow, Gastrointestinal Section, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0NN, United Kingdom.

84

ABSTRACT

The management of inflammatory bowel disease has developed over the last decade with the increasing use of immunosuppressive therapies and a shift away from corticosteroid reliance. As our understanding of the molecular basis of persistent inflammation in the gut advances new and promising medical therapies to treat inflammatory activity are emerging. Anti-tumour necrosis factor therapies form the most significant strategy so far but the targeting of adhesion molecules and use of growth peptides offer alternative approaches. Targeting other novel pro-inflammatory cytokines such as IL-12p40 also appears to be promising. Despite their high initial cost, biological therapies have the potential to reduce hospitalisation and surgery and improve quality of life. Much of the initial success of biological therapies has been in Crohn's disease, and use in ulcerative colitis still remains exploratory. We review the biological basis for these potential therapies and the evidence supporting their use focusing particularly on human studies.

INTRODUCTION

Development of new therapies in inflammatory bowel disease (IBD) has relied heavily on understanding of the molecular pathogenesis of chronic inflammation either in a generic sense, or specifically for the intestinal mucosa. Key roles of cytokines, immune cells and luminal bacterial flora have been elucidated. This has resulted in a wide variety of large and small molecules, which have been subjected to clinical trials in patients, and a substantially larger number of molecules being tried in experimental animals. This review is predominantly focused on human studies.

Conventional therapy with corticosteroids is disappointing in the long term and associated with considerable adverse effects. In the last decade the management of IBD has altered rapidly with a more widespread and aggressive use of immunosuppressive medications such as 6-mercaptopurine/ azathioprine and methotrexate. Furthermore, less reliance is placed on corticosteroids, especially in paediatric practice where defined formula diets are widely used. This review is focused on new and emerging medical therapies to treat inflammatory activity, but it is important to consider the different components of analysis of this complex disease to decide on the optimal course of management. Inflammatory activity as the basis of symptoms has to be distinguished from purely mechanical problems, complications, iatrogenic problems and psychological distress. The term biological agent is often used to refer to engineered synthetic antibodies, cytokines and growth factor peptides with potent effects on the immune system and repair processes. Nucleic acid based therapies such as antisense

oligonucleotides and gene therapies may also be included under the umbrella term of biological agents.

ANTI-TNF THERAPIES

Background

Anti-tumour necrosis factor (TNF) therapy has been most studied amongst biological therapies in inflammatory bowel disease (IBD). Anti-TNF strategies include chimeric monoclonal antibody (infliximab), humanized monoclonal antibody (CDP 571 and the PEGylated CDP870), fully human monoclonal antibody (adalimumab), p75 fusion receptor protein (etanercept), p55 soluble receptor (onercept) and small molecules such as MAP kinase inhibitors and thalidomide congeners. Such therapies fulfil a felt need in current IBD management armamentarium (Table 1).

Table 1: Biological anti-TNF therapies

- **Anti-TNF antibodies**
 - Infliximab
 - CDP-571
 - CDP-870 (Fab² PEGylated)
 - Adalimumab (fully human)
- **TNF binding proteins**
 - P75 fusion protein (Etanercept)
 - Soluble p55 receptor (Onercept)

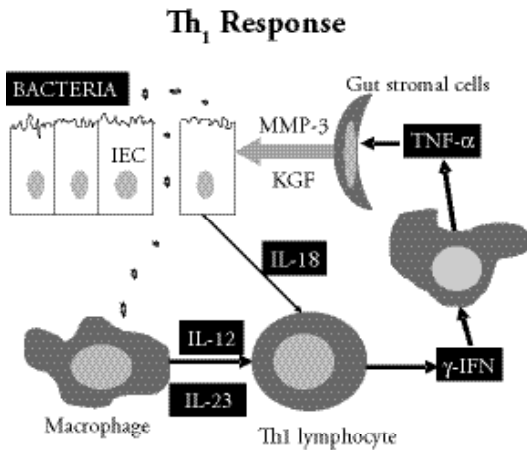


Fig. 1: Bacterial antigen driven macrophage activation and Th1 lymphocyte proliferation in Crohn's disease. The cytokines produced are therapeutic targets for biological therapies.

The role of TNF in Crohn's disease

Crohn's disease (CD) is currently best understood as an activation of lamina propria macrophages and dendritic cells driven by intestinal luminal bacterial antigens leading to a T helper 1 (Th₁) lymphocyte proliferation. TNF has been demonstrated to be elevated in the blood, stool and intestinal tissues of patients with CD.¹ Our current understanding of the immunology of CD is illustrated in Fig. 1.

Mechanism of action of anti-TNF strategies

Apart from neutralising soluble cytokines, monoclonal antibodies may deplete immune cells by a number of mechanisms that include: (a) Antibody-dependent cell-mediated cytotoxicity (ADCC); (b) Complement-dependent cytotoxicity (CDC); (c) Apoptosis of immune cells, lymphocytes or monocytes.

Infliximab binds to both soluble and transmembrane TNF, and also results in lysis of immune cells expressing TNF via CDC and ADCC.^{1,2} Considerable interest has focussed on *in-vitro* and *in-vivo* demonstration of apoptosis of lymphocytes and monocytes in the intestinal lamina propria rapidly after exposure to infliximab.^{3,4} Etanercept neutralises soluble TNF but does not bind to transmembrane TNF. CDP571 neutralises both soluble and transmembrane TNF. Considerable controversy exists about the exact mechanism of action of anti-TNF therapies in different chronic inflammatory conditions.

Chimeric monoclonal antibody to TNF (Infliximab)

Infliximab is a chimeric IgG1 monoclonal antibody that is 75% human and 25% murine. Infliximab has been shown to be effective in the treatment of moderate to severe active and fistulizing CD. The principal use of infliximab is in treating patients not responding to conventional therapies or developing unacceptable side effects. A single infusion of infliximab resulted in impressive short-term response in a 12-week multicenter, double blind placebo controlled trial of infliximab.⁵ A dose of 5mg/kg was most effective, with 81% of patients (Vs 17% receiving placebo) showing a clinical response (decrease in CDAI ≥ 70 points) and 48% (Vs 4% receiving placebo) entering a clinical remission (CDAI < 150) at 4 weeks (Figure 2). Infliximab

Infliximab and Etanercept in the Treatment of Moderate to Severe CD

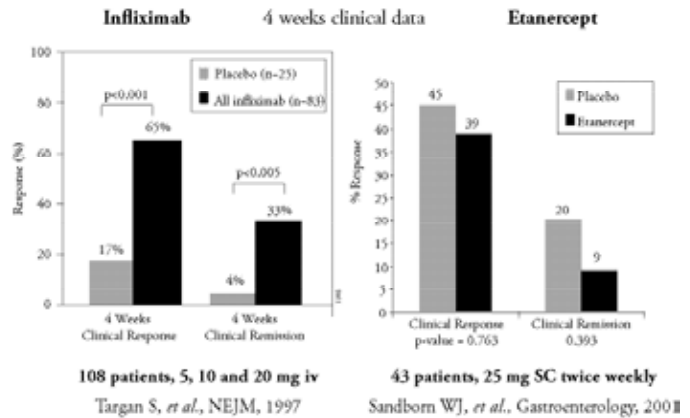


Fig. 2: Short term efficacy of infliximab in terms of clinical response and remission and contrasting lack of efficacy of etanercept.

is steroid-sparing. In the Mayo clinic experience steroids could be discontinued in 73% of patients. Approximately one-third of patients administered a second infusion of infliximab may improve clinically after not responding to a first dose. In a review of infliximab use in Chicago, annual incidence of surgeries were noted to have declined 38%, endoscopies by 43%, radiological examinations by 12% and outpatient GI visits by 20% compared to the year preceding infliximab use. Similar experience has been audited in UK. Such reports are very encouraging raising the potential of overall cost savings in CD patients receiving infliximab.

The demonstration of the efficacy of maintenance therapy every 8 weeks with infliximab in the randomised, controlled, ACCENT I trial on 573 patients opened up the strategy for regular maintenance rather than episodic therapy in CD patients.⁶ In such patients, infliximab therapy if maintained every 8 weeks for 1 year, resulted in a greater likelihood of remaining in remission at weeks 30 and 54, discontinuing corticosteroids, and maintaining response for a longer period of time with a better quality of life. In patients who have failed therapy with corticosteroids and immunosuppressive therapy and are poor surgical candidates, regular maintenance therapy with infliximab is likely to be required. Patients with fistulizing CD, where infliximab therapy is chosen, are also likely to require maintenance therapy. The median time to loss of fistula response was significantly longer for patients treated with infliximab 5mg every 8 weeks (>40 weeks) compared with 14 weeks for placebo-treated patients.⁷ On the other hand, patients with severely active, steroid-refractory CD disease in whom immunosuppressive therapy and infliximab are initiated together, may respond adequately to be continued on long-term immunosuppressive therapy alone. Eight week scheduled therapy groups (5 and 10mg/kg) had fewer hospitalisations, higher rates of mucosal healing (Fig. 3 and 4), and fewer developed antibodies than those in the episodic therapy group.⁸

Immunogenicity is a significant argument against the episodic use of infliximab. The development of antibodies against infliximab is associated with an increased risk of infusion reactions and a reduced duration of response to treatment.⁹ Both concurrent

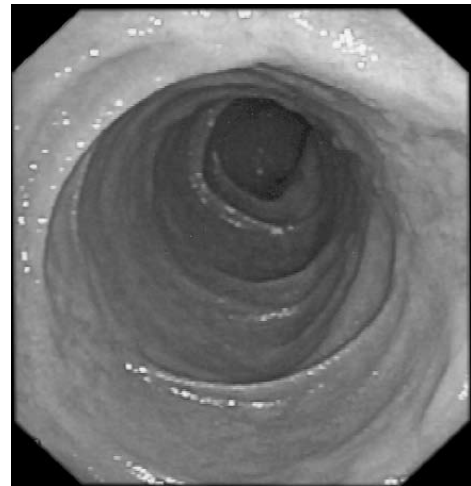
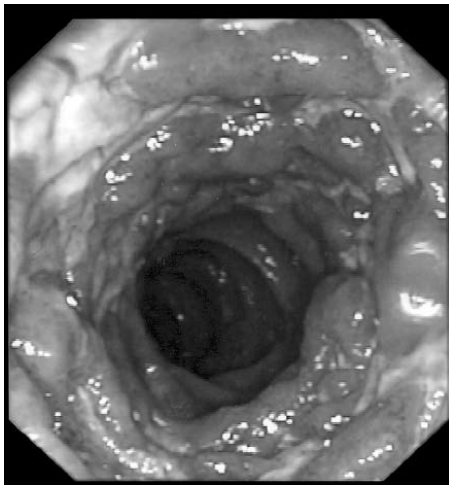


Fig. 3a and 3b: Dramatic mucosal healing at 6 weeks after infliximab administration in Crohn's disease. (a) pre-treatment colonoscopic appearance; (b) post-treatment colonoscopic appearance

Mucosal healing at week 54

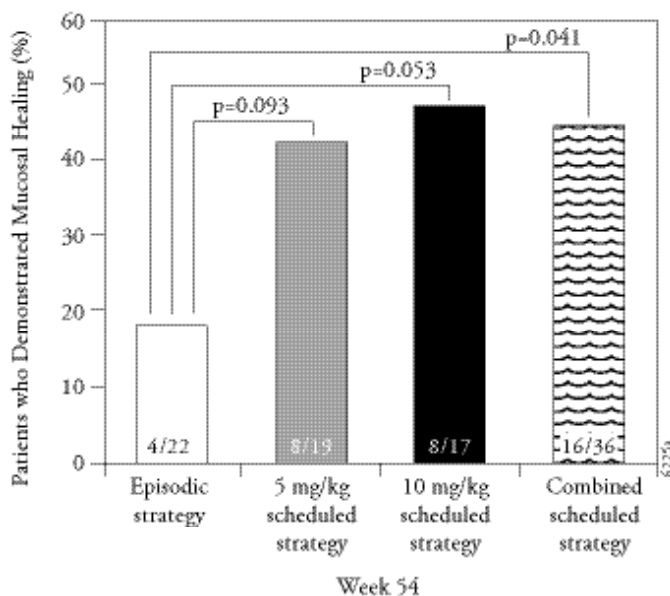


Fig. 4: ACCENT I endoscopic substudy illustrating the benefit of scheduled maintenance therapy in maintaining mucosal healing.

immunosuppressive therapy and intravenous hydrocortisone significantly reduce antibody to infliximab (ATI). Concomitant immunosuppressive therapy reduces the magnitude of the immunogenic response, was predictive of low titers of antibodies against infliximab ($p < 0.001$) and high concentrations of infliximab four weeks after an infusion ($p < 0.001$).

In ulcerative colitis the role of infliximab remains uncertain and large phase III studies are ongoing. Anecdotal and open-labelled pilot studies had reported encouraging results and some encouraging results have also been obtained with other anti-TNF agents such as CDP571. However, in the only sizeable randomised, controlled trial 43 patients with steroid-refractory ulcerative colitis received infliximab or placebo at weeks 0 and 2.¹⁰ At week 6, 39% of infliximab treated patients and 30% of

placebo-treated patients achieved remission ($p = \text{NS}$), and neither the primary endpoint nor a number of secondary endpoints reached statistical significance.

Humanised monoclonal antibody to TNF (CDP571 and CDP870)

CDP571 is a humanised monoclonal IgG4 antibody to TNF with approximately 95% human residues. The 5% murine part is the complementarity determining region (CDR) within the variable region. Initial dose-ranging studies suggested that 10mg/kg of CDP571 was the most effective dose for short term clinical response, with a trend towards maintenance of remission efficacy.¹¹ In a 16-week study¹² in which 396 adult active CD patients (CDAI 220-450) were randomised to receive intravenous CDP571 10mg/kg ($n = 264$) or placebo ($n = 132$) twice the proportion of patients discontinued steroids on CDP571 (20mg/kg at baseline followed by 10mg/kg at week 8) compared with placebo (44% Vs 22%; $p < 0.05$).

CDP 870 is a Fab fragment of a humanized anti-TNF monoclonal antibody with addition of polyethylene glycol to increase the plasma half-life. In a phase II randomised, placebo-controlled study 292 adult patients with active CD (CDAI 220-450) received subcutaneous CDP870 (100, 200 or 400mg) or placebo administered at weeks 0, 4 and 8 weeks. Clinical response rates (decrease in CDAI ≥ 100) were highest in the 400mg CDP870 treatment group at all time points with onset evident at week 2.¹³ Multivariate analysis identified baseline CRP as predictive of significant response. Only 41% of patients had baseline CRP $\geq 10\text{mg/L}$. In this subgroup CDP870 400mg induced significantly higher clinical response and remission rates compared to placebo. Week 12 clinical response was 53.1% (17/32) Vs placebo 17.9% (5/28) [$p = 0.005$].

Fully human monoclonal antibody to TNF (Adalimumab)

Adalimumab (D2E7) is a fully human IgG1 monoclonal antibody. Phase II trials have recently completed to determine the efficacy of adalimumab for the treatment of active CD, and phase III studies are ongoing.

Lymphocyte Trafficking in IBD

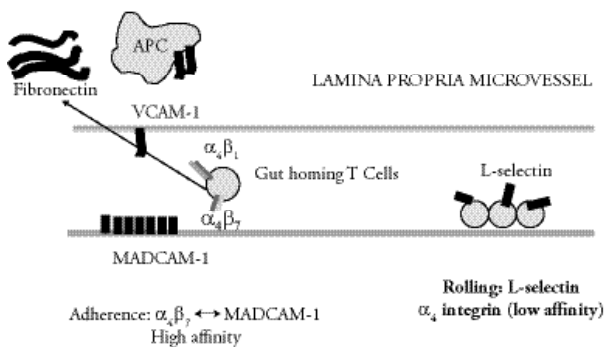


Fig. 5: Schematic diagram showing key molecules involved in lymphocyte trafficking to intestinal mucosa.

Soluble TNF receptor strategies (Etanercept and Onercept)

Etanercept is a completely human fusion protein consisting of the human soluble TNF receptor (p75) linked to Fc portion of an IgG1 antibody. Etanercept has been shown to be ineffective in the treatment of CD¹⁴ (Fig. 2).

Onercept is a soluble human TNF receptor (p55). Administration of 50mg three times per week for 12 weeks showed clinical remission (CDAI<150) in 67% of patients in a small study.¹⁵ Results from a larger phase II placebo-controlled study are disappointing and soluble TNF receptor strategies may not appear to be effective in CD, unlike rheumatoid arthritis or ankylosing spondylitis.

Anti-TNF therapy in extra-intestinal manifestations of CD

Both infliximab and etanercept are effective in ankylosing spondylitis. Infliximab results in rapid improvement and a durable response for at least a year.¹⁶ Anecdotal reports also demonstrate encouraging efficacy in healing pyoderma gangrenosum.

Prediction of response

Non-smoking and concurrent immunosuppressive use are associated with a higher rate of response and longer duration of response.¹⁷ In particular NOD2/CARD15 genotype does not influence response to infliximab in CD.¹⁸ Response appears to be best in patients with elevated C-reactive protein levels.

Safety issues with anti-TNF therapy

Serious and opportunistic infections may occur after anti-TNF therapy. Tuberculosis, histoplasmosis, listeriosis and aspergillosis with infliximab and etanercept have been reported in rheumatoid arthritis. Tuberculosis generally manifests itself within the first six months of therapy, and represents re-activation of latent tuberculosis. Current screening involves a chest radiograph and tuberculin skin testing prior to initiation of infliximab. Of 500 CD patients treated with infliximab at the Mayo Clinic¹⁹ 4% had serious infections attributable to infliximab with 4 deaths.

Antibodies to infliximab (ATI) were reported to be present in 28% of patients in an integrated safety data set including both Crohn's disease and ulcerative colitis.²⁰ Infusion reactions

Table 2: Pre-infliximab administration checklist. Do not administer in the presence of the following:

STOIC

- S= sepsis
- T= TB
- O= Optic neuritis
- I= Infusion reaction
- C= Cancer

following administration occur in 17% of patients treated with infliximab compared with 7% treated with placebo. However, these reactions can be prevented or treated in nearly all patients upon re-treatment.²¹ Autoantibody formation such as antinuclear antibody (34%) and anti-double stranded DNA (9%) rarely lead to drug-induced lupus. Currently the safety data regarding the risk of malignancy appears reassuring despite at least four patients each with Crohn's disease and rheumatoid arthritis developing non-Hodgkin's lymphoma. Chronic inflammatory diseases are associated with an increased baseline risk of malignant lymphoma. Infliximab may exacerbate demyelinating disorders, and rarely may be associated with a new demyelination disorder.

Careful adherence to a checklist (Table 2) can reduce adverse events to anti-TNF therapy.

SELECTIVE ADHESION MOLECULE INHIBITORS

Background

Integrins form a large family of transmembrane proteins required for cell adhesion, morphogenesis, migration, attachment to the extracellular matrix or other cells and to anchor the cytoskeleton to the plasma membrane. Integrins consist of two noncovalently bound α and β subunits. The α_4 chain in association with the β_7 chain defines an integrin subfamily specifically involved in the interaction of lymphocytes with the intestinal mucosa. $\alpha_4\beta_7$ integrin is widely expressed in the intestine and is present on the majority of lamina propria T cells and IgA secreting B cells. The main ligand for $\alpha_4\beta_7$ is mucosal vascular addressin cell-adhesion molecule 1 (MAdCAM-1) but other ligands include fibronectin, VCAM-1 and α_4 integrin itself. α_4 integrin in the low affinity state, as well as L-selectin plays a role in rolling of the lymphocytes in intestinal vascular epithelium, interacting with a number of ligands including MAdCAM-1.²² Activating signals to the lymphocytes result in high affinity state $\alpha_4\beta_7$ expression which results in arrest and adhesion of lymphocytes to the vascular endothelium via MAdCAM-1. Each of these steps is sequentially essential for lymphocyte trafficking into the lamina propria. In addition to lymphocyte homing α_4 integrins are necessary for lymphocyte activation and signalling as well as interaction with extracellular matrix proteins such as fibronectin. These processes are illustrated in Fig. 5.

Natalizumab

Activated lymphocytes and monocytes express α_4 integrin as a dimer with β_1 or β_7 integrin. These molecules dictate the directed trafficking of lymphocytes from the circulation into tissues. $\alpha_4\beta_1$ integrin recognizes VCAM-1 which is upregulated on inflamed endothelium. $\alpha_4\beta_7$ integrin binds MAdCAM-1 and

Lymphocyte Trafficking in IBD

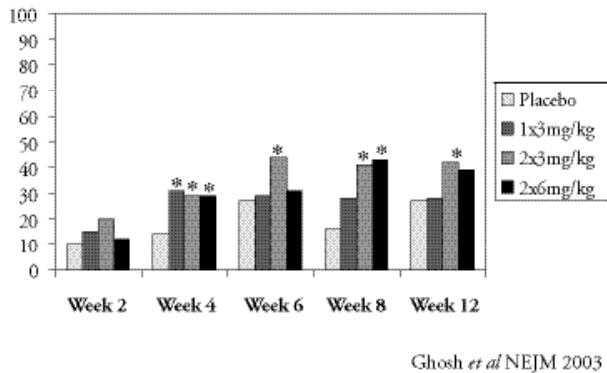


Fig. 6: Rates of remission (Crohn's disease Activity Index <150) after different doses of natalizumab infusion compared with placebo (* represents statistically significant difference compared with placebo). (ref 25)

facilitates the entry of leukocytes into the inflamed intestinal tract. The MAdCAM-1 - $\alpha_4\beta_7$ interaction is most relevant to CD pathogenesis by accumulation of activated lymphocytes in inflamed intestinal wall. Natalizumab is a recombinant IgG₄ humanized monoclonal antibody against α_4 integrin. Natalizumab involves a murine monoclonal ab (AN100226m) which was raised against human α_4 integrin. A humanized anti- $\alpha_4\beta_7$ integrin antibody, LDP-02 has been used in ulcerative colitis.

Animal studies

The proof of concept of effectiveness of α_4 integrin blockade was obtained in cotton-top tamarins that develop spontaneous colitis.^{23,24} It showed improvement of diarrhoea and a reduction of leukocyte infiltration in mucosal biopsies.

Pivotal phase II study in Crohn's disease

In a large placebo-controlled randomised multicentre trial²⁵ of natalizumab in CD, 248 patients with moderate to severe CD were randomized to two infusions of placebo, one infusion of 3mg/kg of natalizumab followed by placebo, two infusions of 3mg/kg of natalizumab or two infusions of 6mg/kg of natalizumab. The group given two infusions of 6mg/kg (n=51) had significantly higher rates of remission at 4 and 8 weeks (29% and 39%) compared with the placebo group (14% and 27%). However the remission rate at 6 weeks compared to placebo did not reach statistical significance (31% Vs 27%). The group given two infusions of natalizumab 3mg/kg (n=66) had significantly higher rates of remission at weeks 4 (29% Vs 14%), 6 (44% Vs 27%) and 8 (41% Vs 16%) compared with placebo (Figure 6). The rate of clinical response was significantly higher in all three natalizumab groups at weeks 4, 6 and 8, with the highest rate (71%) occurring at 6 weeks in the group given two infusions of 3mg/kg. All three active treatment groups showed significant improvement in their inflammatory bowel disease quality of life (IBDQ) at week 6 compared with placebo.

Phase III studies

Natalizumab is not currently licensed for use in CD or multiple sclerosis. A large phase III study in CD has been completed, and

preliminary results have been presented in abstract form.²⁶ Nine hundred five active CD patients with CDAI between 220 and 450 were recruited. In a 4:1 randomization, 724 patients received natalizumab and 118 patients received placebo every 4 weeks for a total of three intravenous infusions (ENACT-1). Though the primary efficacy week 10 endpoint (> 70 points reduction from baseline CDAI) did not achieve significance, there were significant response and remission (CDAI <150) rates at week 12. Week 12 response and remission rates were 62% and 40% respectively, significantly higher (p<0.05) than the 53% and 31% observed with placebo. The mean CDAI change was significantly greater for natalizumab as compared to placebo from 2weeks. Patients on either immunosuppressive therapy at baseline or with prior infliximab therapy had a significantly higher response at week 10 on natalizumab compared to placebo. Patients with evidence of active inflammation at baseline as evidenced by elevated C-reactive protein and platelet count showed significant response and remission rates when administered natalizumab (n=401) compared with placebo (n=107).

Safety and tolerability

Treatment with natalizumab was well tolerated in the phase II study in CD. Antibodies to natalizumab were detected in 7% of patients. During the study period 26 patients had serious adverse events – 7 in the placebo group (11%) – none were considered to be causally related to natalizumab infusion. Natalizumab is effective and well-tolerated treatment for moderate to severe active CD.

Other anti-leukocyte trafficking strategies

Other strategies specifically designed to inhibit adhesion molecules include ICAM-1, $\alpha_4\beta_7$ integrin and the chemokine receptor CCR9 as target molecules. Clinical trials with antisense oligonucleotides to ICAM-1 (ISIS-2302) have been conducted in active Crohn's disease patients.^{27,28} A clinical trial with humanized anti- $\alpha_4\beta_7$ integrin antibody (LDP-02) has been carried out in ulcerative colitis (28 patients in four active treatment and a placebo group) and this dose finding safety study found an encouraging clinical response using a dose of 0.5mg/kg intravenously.²⁹

PEPTIDE GROWTH FACTORS

Background

An increasing number of regulatory peptides expressed in the gastro-intestinal tract have been identified which act in an autocrine fashion in the maintenance of mucosal integrity and repair.^{30,31} On the basis of structural homology several distinct families of peptides have been characterised including the epidermal growth factor family (EGF), the transforming growth factor beta (TGF- β) family, the trefoil factor family (TFF) and the fibroblast growth factor (FGF) family. These peptides function by binding specific cell-surface receptors on adjacent cells and several members within a family may bind to each specific receptor. Multiplicity of function is achieved within families as each factor is produced by several cell populations. Modulation of one family by another is enabled by the ability of cells to express receptors for more than one family. Considerable redundancy is inherent within this complex network of peptides.

Epidermal growth factor

EGF is the best characterised of these growth factors and is a potent stimulator of cell growth and migration.³² In animal models EGF also reduces injury and stimulates repair. The location of the EGF receptor on the basolateral surface would enable ligand binding only after gut injury results in receptor exposure. This has led to the suggestion that EGF acts within the lumen in a surveillance capacity initiating repair mechanisms. In a randomized, double-blind clinical trial 12 patients with mild-to-moderate left-sided ulcerative colitis received daily enemas of 5 µg of EGF in 100 ml of an inert carrier and 12 received daily enemas with carrier alone for 14 days. After two weeks, 10 of the 12 patients given EGF enemas were in remission, as compared with 1 of 12 in the control group (83 percent vs. 8 percent, $P < 0.001$). At the 2-week assessment, disease-activity scores, sigmoidoscopic score, and histological scores were all significantly better in the EGF group than in the placebo group ($P < 0.01$ for all comparisons), and this benefit was maintained at 4 weeks and 12 weeks.

Other growth factors

Other agents, which have shown some evidence of efficacy in pilot studies or anecdotal case reports, include human growth hormone, human granulocyte colony-stimulating factor (filgrastim) and human granulocyte-macrophage colony stimulating factor (GM-CSF, sargramostim). Larger studies with GM-CSF in Crohn's disease are underway.

OTHER BIOLOGICAL THERAPIES

Interleukin-10 (IL-10)

IL-10 inhibits effector functions of activated macrophages and monocytes and down regulates the production of pro-inflammatory cytokines. In a 24-week multicenter prospective, randomized, double blind study 95 active CD patients were treated with subcutaneous, recombinant human IL-10 (rhuIL-10: 1,5,10 or 20 µg/kg) or placebo once daily for 28 consecutive days. Intent-to-treat analysis showed that 23.5% of patients receiving 5 µg/kg rhuIL-10 experienced clinical remission and endoscopic improvement compared with 0% of patients in the placebo group.³³ Subcutaneously administered rhuIL-10 (4µg/kg once daily X 12 weeks or 8 µg/kg twice weekly or placebo) within 2 weeks of ileal or ileocolonic resection did not prevent endoscopic recurrence of CD.³⁴ In another study, though doses of up to 8µg/kg were well tolerated, improvement was modest.³⁵ The concept of a more sustained and focused delivery of IL-10 to gastrointestinal mucosa has been successfully tested in mice models using adenoviral vectors encoding murine IL-10.³⁶

Interleukin-12 (IL-12) neutralising antibody

IL-12 and IL-18 are produced by activated monocytes, macrophages and dendritic cells that drive differentiation of T lymphocytes into a Th₁ phenotype. A clinical trial in CD disease is underway with a human anti IL-12p40 IgG₁ antibody and the phase II dose finding study has demonstrated efficacy, and a monoclonal antibody to human IL-18 is now available for trial in CD.

Interferon-γ (IFN-γ) neutralising antibody

Production of IFN-γ is a hallmark of Th₁ T lymphocytes and increased IFN-γ production is found in CD. Uncontrolled studies show that subcutaneous interferon α-2A might be beneficial in CD, and uncontrolled studies with interferon α-2B have reported response rates ranging from 33-50% in CD. A pilot study with interferon β in five CD patients, which is used to treat multiple sclerosis, reported improvement in 80%. A phase II study using IFN-γ neutralising monoclonal antibody is investigating its therapeutic efficacy and the initial reports give mixed results.

Interferon-11 (IL-11)

This is produced by the stromal cells and acts to maintain the integrity of epithelial cells and reduce pro-inflammatory cytokines. IL-11 was evaluated in a multicenter study on active CD patients and a higher rate of response was noted in the treatment group (16µg/kg dose) compared with the placebo group.³⁷

CONCLUSION

A number of biological agents show promise in being effective anti-inflammatory therapy in IBD. However, most of these agents will be expensive and the search for small, inexpensive molecules continue. Natalizumab, CDP870 and adalimumab are probably the agents most likely to join infliximab as a biological therapeutic option in active CD, but the exact place of these therapies in IBD will continue to evolve over the next few years. Despite the upfront cost of biological therapy, cost-effectiveness studies may demonstrate significant pharmacoeconomic benefits by reducing hospitalizations and surgeries. Such studies are likely to attract considerable attention in the next decade. The ever-increasing use of infliximab is setting new standards of therapy in CD and the new therapies currently in evolution will have to improve upon it in efficacy, tolerability and pharmacoeconomics. This is unlikely to happen for quite some time and newer agents will tend to be used in patients who are resistant to infliximab or show loss of response.

REFERENCES

1. Papadakis KA, Targan SR. Tumour necrosis factor: biology and therapeutic inhibitors. *Gastroenterology* 2000;119:1148-1157.
2. Scallon BJ, Moore MA, Trinh H, et al. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. *Cytokine* 1995;7:251-259.
3. Luger A, Schmidt M, Luger N, et al. Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. *Gastroenterology* 2001;121:1145-1157.
4. Ten Hove T, van Montfrans C, Peppelenbosch MP, van Deventer SJ. Infliximab treatment induces apoptosis of lamina propria T lymphocytes in Crohn's disease. *Gut* 2002;50:206-211.
5. Targan SR, Hanauer SB, van Deventer SJH, Mayer et al. A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor α for Crohn's disease. *New Engl J Med* 1997;337:1029-1035.
6. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541-1549.
7. Sands B, van Deventer S, Bernstein C, et al. Long-term treatment of fistulizing Crohn's disease: response to infliximab in the ACCENT II trial through 54 weeks. *Gastroenterology* 2002;122:A81.
8. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;126:402-13.

9. Baert F, Norman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601-608.
10. Probert CSJ, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003;52:998-1002.
11. Sandborn WJ, Feagan BG, Hanauer SB, et al. An engineered human antibody to TNF (CDP571) for active Crohn's disease: a randomised double-blind placebo-controlled trial. *Gastroenterology* 2001;120:1330-1338.
12. Feagan BG, Sandborn WJ, Baker J, et al. A randomised, double-blind, placebo-controlled, multi-center trial of the engineered human antibody to TNF (CDP571) for steroid sparing and maintenance of remission in patients with steroid-dependent Crohn's disease. *Gastroenterology* 2000;118:A655.
13. Schreiber S, Rutgeerts P, Fedorak R, et al. CDP870, a humanized anti-TNF antibody fragment, induces clinical response with remission in patients with active Crohn's disease. *Gastroenterology* 2003;124 (suppl 1):A61.
14. Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomised, double-blind, placebo-controlled trial. *Gastroenterology* 2001;121:1088-1094.
15. Rutgeerts P, Lemmens L, Van Assche G, et al. Recombinant soluble p55 receptor induces remission, is non-immunogenic and well tolerated in active Crohn's disease: results of a randomised pilot trial. *Gastroenterology* 2001;120:A452.
16. Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis. *Arthritis and Rheumatism* 2003;48:2224-2233.
17. Parsi MA, Achkar J-P, Richardson S, et al. Prediction of response to infliximab in patients with Crohn's disease. *Gastroenterology* 2002;123:707-713.
18. Vermeire S, Louis E, Rutgeerts P, et al. NOD2/CARD15 does not influence response to infliximab in Crohn's disease. *Gastroenterology* 2002;123:106-111.
19. Colombel J-F, Loftus EV, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease. *Gastroenterology* 2004;126:19-31.
20. Schaible TF. Long term safety of infliximab. *Canadian J Gastroenterol* 2000;14(supplement C):29C-32C.
21. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003;98:1315-1324.
22. Rutgeerts P, Van Deventer S, Schreiber. Review article: the expanding role of biological agents in the treatment of inflammatory bowel disease - focus on selective adhesion molecule inhibition. *Aliment Pharmacol Ther* 2003;15:17:1435-50
23. Podolsky DK, Lobb R, King N, et al. Attenuation of colitis in the cotton-top tamarin by anti-alpha 4 integrin monoclonal antibody. *J Clin Invest* 1993;92:372-380.
24. Hesterberg PE, Winsor-Hines D, Briskin MJ, et al. Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to gut-homing integrin $\alpha_4\beta_7$. *Gastroenterology* 1996;111:1373-1380.
25. Ghosh S, Goldin E, Gordon F, et al. Natalizumab for active Crohn's disease. *N Engl J Med* 2003;348:24-32.
26. Rutgeerts P, Colombel J, Enns R, et al. Subanalysis from a phase 3 study on the evaluation of natalizumab in active Crohn's disease therapy (ENACT1). *Gut* 2003;52(suppl VI):A239.
27. Yacychyn BR, Bowen-Yacyshyn MB, Jewell L, et al. A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease. *Gastroenterology* 1998;114:1133-1142.
28. Schreiber S, Nikolaus S, Malchow H, et al. Absence of efficacy of subcutaneous antisense ICAM-1 treatment of chronic active Crohn's disease. *Gastroenterology* 2001;120:1339-1346.
29. Feagan BG, McDonald J, Greenberg G, et al. An ascending dose trial of a humanized $\alpha_4\beta_7$ antibody in ulcerative colitis (UC). *Gastroenterology* 2000;118:A874
30. Dignass AU, Sturm A. Peptide growth factors in the intestine. *Euro J Gastroenterol & Hepatol* 2001;13:763-770.
31. Podolsky DK. Mucosal immunity and inflammation. V. Innate mechanisms of mucosal defense and repair: the best offense is a good defense. *Am J Physiol* 1999;277(3 Pt 1):495-9.
32. 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;24;49:350-7.
33. Fedorak RN, Gangl A, Elson CO, et al. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. *Gastroenterology* 2000;119:1781-1783.
34. Colombel JF, Rutgeerts P, Malchow H, et al. Interleukin 10 (Tenovil) in the prevention of postoperative recurrence of Crohn's disease. *Gut* 2001;49:42-46.
35. Schreiber S, Fedorak RN, Nielsen OH, et al. Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. *Gastroenterology* 2000;119:1461-1472.
36. Lindsay JO, Ciesielski CJ, Scheinin T, et al. Local delivery of adenoviral vectors encoding murine interleukin 10 induces colonic interleukin 10 production and is therapeutic for murine colitis. *Gut* 2003;52:363-369.
37. Sands BE, Bank S, Sninsky CA, et al. Preliminary evaluation of safety and activity of recombinant human interleukin 11 in patients with active Crohn's disease. *Gastroenterology* 1999; 117: 58-64.