Anti-tumour necrosis factor-α therapies in Crohn's disease

This article reviews the limitations of existing Crohn's disease therapies and the efficacy and safety of anti-tumour necrosis factor-α drugs. Trying to determine which patients may benefit from these therapies while minimizing toxicity is key. Special treatment situations and future developments are also briefly discussed.

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract. Clinical features of Crohn's disease include abdominal pain, diarrhoea, weight loss, anaemia and transmural inflammation of the gastrointestinal tract interspersed by skip lesions of normal mucosa. The incidence of Crohn's disease is increasing, with high relapse rates in untreated disease. Approximately 80% of Crohn's disease patients will require surgery within 10 years of diagnosis. Quality of life scores are impaired in patients with Crohn's disease.

At the molecular level Crohn's disease is characterized by the excessive production, in both the blood and gut mucosa, of a number of pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α) (Stevens et al, 1992). Therapies targeting and blocking the molecular effects of these cytokines have been developed in recent years. Of these, anti-TNF-α monoclonal antibody therapies have had the greatest success and are now widely used in the management of Crohn's disease.

Limitations of existing Crohn's disease therapies

Several classes of pharmacological agents may be used in patients with Crohn's disease. Traditionally 5-aminosalicylate compounds have been widely used, but the evidence for efficacy of these drugs, particularly as a maintenance therapy, is very limited (Akobeng and Gardener, 2005). Corticosteroids may have a valuable role in inducing remission in inflammatory relapses of Crohn's disease, but are ineffective as a maintenance therapy. Steroid use is associated with increased morbidity and mortality compared with immunomodulator and biological therapies (TREAT – Crohn's disease Therapy, Resource, Evaluation, and Assessment Tool – registry; Lichtenstein et al, 2006). Azathioprine and methotrexate are the two most commonly used immunomodulator therapies in steroid-resistant or dependent disease although tacrolimus and mycophenolate have both been used. There is evidence that these agents improve rates of response and remission in Crohn's disease patients. However, significant numbers of patients will fail these therapies or not tolerate them, and such patients may be considered for biological therapy.

Dr MB Sprakes *is IBD Research Fellow and* **Dr PJ Hamlin** *is Consultant Gastroenterologist in the Department of Gastroenterology, Leeds General Infirmary, Leeds LS1 3EX*

Correspondence to: Dr PJ Hamlin

Anti-TNF-α therapies

Infliximab (Remicade, Centocor, Pennsylvania) and adalimumab (Humira, Abbott, Berkshire) are anti-TNF-α therapies that are both licensed for the treatment of severe, active colonic Crohn's disease and, in the case of infliximab, for fistulating perianal disease. Certolizumab pegol (Cimzia, UCB Pharma, Georgia) is a pegylated humanized Fab' fragment of an anti-TNF-α monoclonal antibody which has demonstrated efficacy in Crohn's disease. This drug has received Food and Drug Administration but not European Medicines Agency approval. The anti-TNF-α fusion protein, etanercept, is used in rheumatoid arthritis but interestingly is not effective in Crohn's disease.

Both infliximab and adalimumab bind to and block the action of membrane-bound and soluble TNF-α leading to diminished cytokine effect and apoptosis of pro-inflammatory cells. Infliximab is a chimeric monoclonal antibody (murine–human) whereas adalimumab is fully humanized, theoretically making it less immunogenic. Infliximab is administered as a 5 mg/kg intravenous infusion, initially over 2 hours, but accelerated infusions lasting 30 minutes are safe and well tolerated (Donnellan et al, 2009). Adalimumab is delivered as a subcutaneous injection with a license for 80 mg followed by 40 mg every other week. The current National Institute for Clinical Excellence (2002) position statement for infliximab says that it should be reserved for patients who have severe active Crohn's disease which is refractory to treatment with immunomodulatory drugs and where surgery is deemed inappropriate such as those with diffuse disease or risk of short bowel syndrome. The National Institute for Health and Clinical Excellence position with regard to infliximab and adalimumab is currently under review with particular concern expressed by gastroenterologists and patient groups (National Association of Colitis and Crohn's Disease) who advocate the use of scheduled maintenance therapy. Fortunately the initial appraisal document supports the use of maintenance therapy.

Efficacy

A 12-week multicentre, double-blind, placebo-controlled trial of infliximab in 108 patients was conducted in 1997 which confirmed the efficacy of infliximab, with a third of patients being in remission at 3 months following a single infusion (Targan et al, 1997).

The ACCENT I study in 2002 demonstrated the sustained benefits of scheduled 8-weekly infliximab therapy (Hanauer et al, 2002) and the subsequent ACCENT II study continued to support the efficacy of infliximab, in this instance promoting healing in fistulating disease (Sands et al, 2004). Furthermore maintenance therapy with infliximab decreases the number of hospitalizations and surgical procedures for Crohn's disease when compared to episodic therapy (Rutgeerts et al, 2004). Maintenance therapy also significantly improves the Crohn's disease activity index and limits the formation of antibodies to infliximab which are associated with loss of response. The safety profile of infliximab does not differ between the maintenance and episodic groups.

The 'top-down' approach with early use of infliximab therapy in steroid- and immunomodulator-naive patients has demonstrated improved remission rates as compared to the traditional 'step-up' approach of steroids followed by azathioprine with biological therapy reserved for refractory cases (Hommes et al, 2006). The top-down approach is steroid sparing and leads to improved mucosal healing. Mucosal healing may imply a more complete remission and is associated with reduced hospitalizations and need for surgery (Schnitzler et al, 2009). Certain clinical parameters such as young age of onset, extensive disease, perianal disease and need for steroids at first diagnosis may help to identify groups of patients who will benefit most from early use of biological therapies (Beaugerie et al, 2006).

The SONIC study compared the efficacy of azathioprine *vs* infliximab *vs* combined azathioprine and infliximab in immunomodulator- and biologic-naive patients (Colombel et al, 2009). Week 26 steroid-free remission was the primary endpoint. Patients receiving azathioprine in combination with infliximab had the highest rate of remission (57%) compared with infliximab alone (44%) or azathioprine alone (30%). Mucosal healing at week 26 was shown in 43.9% of the patients treated with infliximab + azathioprine, 30.1% of those treated with infliximab alone, and 16.5% of those treated with azathioprine. Sub-group analysis demonstrated that the greatest remission rates were achieved in those patients with an elevated C-reactive protein level and mucosal ulceration at baseline.

The CLASSIC 1 trial was a double-blind randomized control trial investigating the efficacy of adalimumab induction at increasing dosage against placebo in 299 biologic-naive patients (Hanauer et al, 2006). Patients were randomized to receive either adalimumab 40 mg at week 0 and 20 mg at week 2, 80 mg at week 0 and 40 mg at week 2, 160 mg at week 0 and 80 mg at week 2 or placebo at week 0 and week 2 with assessment of primary endpoints at week 4. All dosage regimens were superior in terms of remission compared to placebo therapy, with those taking the highest dose showing a significant difference in remission rates at week 4. Benefit of maintenance therapy with adalimumab was demonstrated in the CLASSIC II (Sandborn et al, 2007a) and CHARM trials (Colombel et al, 2007).

The CHARM study was an open label induction period (80 mg at week 0 with 40 mg at week 2) followed by randomization (of responders and non-responders) to 40 mg every other week, 40 mg weekly or placebo in moderate or severe Crohn's disease. At week 12 non-responders could receive open label 40 mg every other week or escalate to 40 mg weekly. Remission rates for randomized responders were 40% (40 mg every other week) and 47% (40 mg weekly) at week 26 and 36% (40 mg every other week) and 41% (40 mg weekly) at week 56 respectively. There was no significant difference between adalimumab delivered as a weekly therapy as opposed to every other week but each regimen was superior to placebo. An open label extension of the CHARM study demonstrated sustained steroid-free remission at 2 years for 80% of patients in remission after 1 year of adalimumab therapy.

The GAIN study (Sandborn et al, 2007b) evaluated the efficacy of adalimumab in patients who had previously failed infliximab therapy with significantly improved response and remission rates (51.6% and 21.4% respectively) compared to placebo at week 4. Current expert opinion suggests optimizing the initial biologic therapy by dose increase or shortened infusion times (from 8 to 6 weeks in the case of infliximab for example) before switching between the drugs (unlicensed indication).

Safety

The side-effect profiles of infliximab and adalimumab are broadly similar. The safety profile of infliximab has been prospectively evaluated by the TREAT registry (Lichtenstein et al, 2006). Over 6000 patients have enrolled with approximately 50% having been treated with infliximab and 50% biologic-naive receiving other therapies. Using multivariate logistical regression, only steroid use was documented to increase the risk of mortality, while the use of steroids or opiate analgesia was associated with increased risk of serious infections. However, there are recognized complications of anti-TNF-α therapy. The Mayo clinic experience of 2004 (Colombel et al, 2004) monitored adverse events following infliximab therapy in 500 consecutive patients. They found 6% of patients had a serious adverse event related to infliximab, which included infusion reactions, lupus-like reactions, delayed hypersensitivity and demyelination, and 8% of patients had infections attributed to infliximab, with two fatal episodes of sepsis. Three

patients developed malignancy that may have been related to infliximab. Excluding tuberculosis infection and vaccinating against preventable opportunistic infections before infliximab therapy is recommended (Rahier et al, 2009).

Concomitant use of other immunomodulators, such as azathioprine, with infliximab has also raised concerns about the development of hepatosplenic T cell lymphoma, a very rare form of lymphoma. This has been seen in patients with Crohn's disease given infliximab along with either mercaptopurine or azathioprine and is almost always fatal (Mackey et al, 2007). Recent data are casting doubt over the rationale for persisting with immunomodulator therapy alongside infliximab after the initial 6 months of therapy in patients who had been unresponsive to azathioprine monotherapy before the introduction of infliximab. Beyond 6 months there is little difference in antibodies to infliximab formation and hence secondary loss of response in groups receiving infliximab as monotherapy compared to dual therapy. Longer term data from the SONIC study will help to clarify whether dual therapy with azathioprine and infliximab (in patients previously naive to both drugs) has sustained benefit over infliximab alone. The trials for adalimumab suggest monotherapy is as effective as combined therapy but there is also a case report of hepatosplenic T cell lymphoma in a patient with rheumatoid arthritis treated with adalimumab monotherapy (Shale et al, 2008). A careful assessment of risk and benefit of these therapies for patients with Crohn's disease must always be undertaken.

Special situations

Anti-TNF-α therapies are effective in the treatment of inflammatory bowel disease-associated extra-intestinal manifestations. These include refractory uveitis, pyoderma and seronegative peripheral and axial arthropathies. Patients with these problems may benefit from a lower threshold for introduction of biological therapy as may patients with inflammatory bowel disease associated with other TNF-α-mediated diseases such as psoriasis, psoriatic arthropathy and rheumatoid arthritis.

Female patients with Crohn's disease are more likely to conceive when in clinical remission and more likely to have a successful outcome to pregnancy if they sustain that remission. Anti-TNF-α therapies have a Food and Drug Administration category B rating and current best practice is felt to be to continue these drugs in pregnancy (Caprilli et al, 2006). Infliximab and adalimumab can both cross the placenta and levels of the drugs have been recorded in a small number of neonates who have been studied. Scheduling of these drugs in the third trimester is therefore a balance of risk *vs* benefit and should be discussed between patient, gastroenterologist and obstetrician.

KEY POINTS

- Anti-tumour necrosis factor-α therapies are safe and effective therapies for Crohn's disease.
- Their use as maintenance therapy reduces hospitalizations and the need for surgery.
- 'Top down' therapy in selected patients early in the course of their disease may be appropriate.
- The review of anti-tumour necrosis factor-α therapy for Crohn's disease by the National Institute for Health and Clinical Excellence is eagerly anticipated, with the majority of expert opinion in favour of scheduled maintenance therapy for patients responding to induction therapy.
- Anti tumour necrosis factor-α therapy may be effective therapy for extra-intestinal manifestations such as uveitis, pyoderma and inflammatory bowel disease-associated arthropathy.

Conclusions

Anti-TNF-α drugs are increasingly used in the management of Crohn's disease. Genome-wide scans have identified Crohn's disease to be a hugely polygenic disorder and have enhanced our understanding of the pathogenesis of the disease. The potential for new pathways to be targeted in the development of further therapies will hopefully be realized. There continues to be interest in innate and adaptive immunity, and agents blocking the action of IL-12/23 are being developed. The emergence of defective autophagy pathways in Crohn's disease, with the implication of the autophagy genes ATG16L1 and IRGM in Crohn's disease, is also an exciting area for continued research.

Anti-TNF-α agents are safe and effective therapies for Crohn's disease. In clinical trials two thirds of patients will respond to these therapies with one third achieving remission. Maintenance therapy is clinically superior to episodic therapy and reduces the need for hospitalization and surgery. Maintenance *vs* episodic anti-TNF-α therapy is currently subject to review by National Institute for Health and Clinical Excellence. Quality of life is improved by spending less time in hospital and having fewer operations. In addition, the broader costs of Crohn's disease to the patient and to society need to be recognized. Are patients able to perform the jobs for which they were trained and how many have to claim disability living allowance?

Careful patient selection to establish those who will benefit most from these therapies is vital. At present this relies on clinical parameters of what constitutes severe disease currently or with poor prognostic factors such as young age with extensive disease, need for steroids at first presentation and perianal disease. It is hoped that serology and genotyping for the known disease susceptibility genes may ultimately prove useful but thus far this is not the case. There is no doubt that new biological therapies will be introduced into inflammatory bowel disease treatment strategies in the future. The goals for clinicians and their patients continue to be maximizing quality of

life, establishing steroid-free remission and timely introduction of therapies which modify the natural history of the disease while minimizing toxicity. **BJHM**

Conflict of interest: Dr PJ Hamlin has been on advisory boards for both Schering Plough and Abbott Pharmaceuticals. Schering Plough support an IBD clinical nurse specialist post at Leeds General Infirmary.

Akobeng AK, Gardener E (2005) Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* **1**: CD003715

Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J (2006) Predictors of Crohn's disease. *Gastroenterology* **130**: 650–6

Caprilli R, Gassull MA, Escher JC et al (2006) European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. European Crohn's and Colitis Organisation. *Gut* **55** (Suppl 1): i36–58

Colombel JF, Loftus EV Jr, Tremaine WJ et al (2004) The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* **126**(1): 19–31

Colombel JF, Sandborn WJ, Rutgeerts P et al (2007) Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* **132**(1): 52–65

Colombel JF, Rutgeerts P, Reinisch W et al (2009) SONIC: a randomized, double-blind, controlled trial comparing infliximab and infliximab plus azathioprine to azathioprine in patients with Crohn's disease naive to immunomodulators and biologic therapy. *J Crohn's Colitis* **3**(1): S45–S46

Donnellan CF, Ford AC, Sprakes MB, Greer D, Fairclough A, Warren L, Hamlin PJ (2009) Accelerated infliximab infusions are safe and well tolerated in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* **21**(1): 71–5

Hanauer SB, Feagan BG, Lichtenstein GR et al (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. ACCENT I Study Group. *Lancet* **359**(9317): 1541–9

Hanauer SB, Sandborn WJ, Rutgeerts P et al (2006) Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* **130**(2): 323–33

Hommes D, Baert F, van Assche G et al (2006) The ideal management of Crohns disease: top down versus step up strategies, a randomized controlled trial. *Gastroenterology* **130**: A-108-109 Abstract 749

Lichtenstein GR, Feagan BG, Cohen RD et al (2006) Serious infection and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* **4**(5): 621–30 (Erratum in: *Clin Gastroenterol Hepatol* **4**(7): 931)

Mackey AC, Green L, Liang LC, Dinndorf P, Avigan M (2007) Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* **44**(2): 265–7

National Institute for Clinical Excellence (2002) *The clinical effectiveness and cost effectiveness of infliximab for Crohn's Disease.* Technology appraisals TA40. National Institute for Clinical Excellence, London

Rahier JF, Ben-Horin S, Chowers Y et al (2009) European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infectionsin inflammatory bowel disease. *J Crohn's Colitis* **3**: 47–91

Rutgeerts P, Feagan BG, Lichtenstein GR et al (2004) Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* **126**(2): 402–13

Sandborn WJ, Hanauer SB, Rutgeerts P et al (2007a) Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* **56**(9): 1232–9

Sandborn WJ, Rutgeerts P, Enns R et al (2007b) Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* **146**(12): 829–38

Sands BE, Blank MA, Patel K, van Deventer SJ; ACCENT II Study (2004) Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol* **2**(10): 912–20

Schnitzler F, Fidder H, Ferrante M et al (2009) Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* **15**(9): 1295–301

Shale M, Kanfer E, Panaccione R, Ghosh S (2008) Hepatosplenic T cell lymphoma in inflammatory bowel disease. *Gut* **57**(12): 1639–41

Stevens C, Walz G, Singaram C et al (1992) Tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 expression in inflammatory bowel disease. *Dig Dis Sci* **37**(6): 818–26

Targan SR, Hanauer SB, van Deventer SJ et al (1997) A short term study of chimeric monoclonal antibody cA2 to tumour necrosis factor alpha for Crohn's disease. Crohn's disease cA2 study group. *N Engl J Med* **337**(15): 1029–35