

Targeting nanomedicines in the treatment of Crohn's disease: focus on certolizumab pegol (CDP870)

Lotte Dinesen
Simon Travis

Gastroenterology Unit,
John Radcliffe Hospital, Oxford, UK

Abstract: A variety of targets for therapeutic intervention are based upon advances in understanding of the immunopathogenesis of Crohn's disease. Crohn's disease is initiated by an innate immune response, which eventuates in a T-cell driven process, characterized by a T-helper cell 1 type cytokine profile. Several new treatments now focus on suppressing T-cell differentiation or T-cell inflammation. Since inflammatory bowel disease (IBD) represents a state of dysregulated inflammation, drugs that augment the anti-inflammatory response have the potential to downregulate inflammation and thereby hopefully modify the disease. Tumour necrosis factor (TNF) is a major target of research and clinical investigation. TNF has proinflammatory effects in the intestinal mucosa and is a pivotal cytokine in the inflammatory cascade. Certolizumab pegol (CDP870) is a PEGylated, Fab' fragment of a humanized anti-TNF-alpha monoclonal antibody. PEGylation increases the half-life, reduces the requirement for frequent dosing, and possibly reduces antigenicity as well. Certolizumab has been shown in Phase III trials to achieve and maintain clinical response and remission in Crohn's disease patients. It improves the quality of life. Certolizumab pegol will be indicated for moderately to severely active Crohn's disease, but it is not yet licensed in Europe or the US. It is not possible to construct an algorithm for treatment, but when compared with infliximab the two principal advantages are likely to be lower immunogenicity (as shown by anti-drug antibodies, absence of infusion reactions, and low rate of antinuclear antibodies), and a subcutaneous route of administration. These two factors may be sufficient to promote it up the pecking order of anti-TNF agents.

Keywords: certolizumab pegol, Crohn's disease, Fab, TNF

Background

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract which primarily affects younger individuals, although 15% of people are over the age of 60 at diagnosis. The natural history is characterized by relapses and remission. It causes patchy, transmural inflammation, which can affect any part of the gastrointestinal tract, although it predominantly affects the distal small bowel (ileum, about 30%), colon (30%), or both (30%). Once established at a particular site, it rarely extends elsewhere (Sands 2004a).

Classification

In clinical practice Crohn's disease is defined by location of disease: terminal ileum, colonic, ileo-colic, perianal, upper gastrointestinal, or by the pattern of disease: inflammatory, fistulating or stricturing. For the purposes of classification, the age of onset (<40 years, or >40 years) and modifiers according to the presence or absence of perianal or upper gastrointestinal disease location have been included (Silverberg et al 2005). Clinical activity at a point in time is classified broadly into remission, mild,

Correspondence: SPL Travis
Gastroenterology Unit, John Radcliffe
Hospital, Oxford, OX3 9DU, UK
Tel +44 1865 851072
Fax +44 1865 220320
Email simon.travis@ndm.ox.ac.uk

moderate, or severely active Crohn's disease (Stange et al 2006; Travis et al 2006). These are not precisely defined entities. Most clinical trials in patients with active Crohn's disease recruit patients with a Crohn's Disease Activity Index (CDAI) >220. The fallibility of this threshold is illustrated by the high placebo response in recent trials of biological therapy (Su et al 2004). Remission is widely accepted as a CDAI <150 and response to any therapy is generally defined as a decrease in CDAI \geq 100 points. It would make sense to define disease activity in groups of 100 points (remission CDAI <150; mild 150–250; moderate 250–350; and severe >350), and future trials may adopt this approach. To put this into clinical context, moderate disease activity is consistent with symptoms of intermittent vomiting, or weight loss >10%, where treatment for mild disease is ineffective, or a tender mass is present without overt obstruction. The C-reactive protein (CRP) is usually elevated above the upper limit of normal. By contrast, severe disease may be manifest by cachexia (BMI <18 kg/m²), evidence of obstruction or abscess, or persistent symptoms despite intensive treatment (Stange et al 2006).

Prevalence

The incidence of Crohn's disease is generally estimated at around 5–10 per 100 000 per year, with a prevalence of 50–100 per 100 000, although this may be an underestimate (Loftus 2004). It is considered to be up to twice as common as ulcerative colitis in adults, although prevalence of the two conditions in children is similar. It is estimated that up to 240 000 people are affected by inflammatory bowel disease (IBD) in the UK (Carter et al 2004).

Pathogenesis

The pathogenesis remains unknown, but is likely to be related to mucosal immune dysregulation, genetic factors, bacterial flora, and other as yet unidentified environmental triggers. The complex interaction of genetic, microbial, and environmental factors culminates in a sustained activation of mucosal immune and non-immune responses, facilitated by defects in the intestinal epithelial barrier and mucosal immune system, resulting in inflammation and cell destruction. In a healthy individual, the intestinal mucosa is in a state of controlled inflammation regulated by a complex balance of proinflammatory (tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, interleukin (IL)-1, IL-6, IL-8 and IL-12) and counterbalanced by anti-inflammatory cytokines (IL-4, IL-10, IL-11 and IL-13). Because inflammatory bowel disease represents a state of dysregulated inflammation, drugs

that can augment the anti-inflammatory response have the potential to downregulate inflammation and thereby improve the disease. Cytokines play a central role in modulating inflammation, and are therefore a target for IBD therapy using specific cytokine inhibitors, such as anti-TNF antibodies (Sands 2004b; Ardizzone and Bianchi Porro 2005; Chang and Lichtenstein 2006; Korzenik 2006).

TNF has diverse proinflammatory effects within the intestinal mucosa and is a pivotal cytokine in the inflammatory cascade. TNF binds to cell receptors with high affinity and specificity. This transmembrane binding of TNF effects apoptosis of T cells, so a fundamental defect in Crohn's disease appears to be dysregulation of T cell populations (Ivashkiv 2003; Sands 2004b; Korzenik 2006). The release of TNF is a crucial early step during innate immunity and the initial response to pathogens, through the induction of the acute inflammatory response. Controlled inflammation is generally beneficial, but if there is too much TNF, or TNF is inappropriately produced, it provokes chronic inflammation, such as in Crohn's disease. This is the premise behind anti-TNF therapy for Crohn's disease.

Conventional therapy

The principal aims of medical treatment are to decrease the inflammatory process, to induce clinical remission when disease is active by promoting mucosal healing, to maintain remission in patients and avoid complications. Conventional therapeutic recommendations for Crohn's disease are determined by the location, pattern, and severity of disease. The European Crohn's and Colitis Organisation (ECCO) recommend budesonide, a steroid with low systemic bioavailability, as first-line treatment for active Crohn's disease (Travis et al 2006). Budesonide 9mg daily is favored because it is superior to both placebo (OR 2.85, 95% CI 1.67–4.87) and mesalazine 4 g/day (OR 2.8, 95% CI 1.50–5.20) (Otley and Steinhart 2005). It achieves remission in 51%–60% over 8–10 weeks (Hanauer et al 2002; Ivashkiv 2003; Sandborn 2003; Sands 2004b; Ardizzone and Bianchi Porro 2005). Budesonide is preferred to prednisolone for mildly active CD because it is associated with fewer side-effects, although a Cochrane systematic review has shown budesonide to be somewhat less effective (pooled OR for the 5 trials 0.69, 95% CI 0.51–0.95) (Otley and Steinhart 2005). Although corticosteroids are effective in suppressing the symptoms, they do not promote mucosal healing and their use is limited by short- and long-term side effects. Patients refractory to or dependent on steroids are candidates for immune modifier treatment with antimetabolites such as

6-mercaptopurine, azathioprine, or methotrexate (Travis et al 2006). Immunomodulators (azathioprine/mercaptopurine, methotrexate) are effective in steroid-dependent Crohn's disease (NNT 3) (Pearson et al 2000; Alfadhli et al 2003). Ileal resection is an alternative, but this should be individualized, according to disease characteristics. Infliximab is best reserved for patients not responding to initial therapy and for whom surgery is considered inappropriate. This does not mean that surgery takes precedence over infliximab. Both the indication and timing are joint decisions between patient, physician, and surgeon. Surgical options should, however, be considered and discussed with the patient as part of an overall management strategy. The stage at which anti-TNF therapy is introduced may change if it can be established that earlier therapy alters the pattern of disease. The use of anti-TNF therapy such as infliximab is governed by national guidelines, such as those from the National Institute for Health and Clinical Excellence (NICE) in the UK (NICE 2002). These frequently fail to keep up with therapeutic trends and professional associations have published more recent, evidence-based guidance (Lichtenstein et al 2006a; Travis et al 2006).

Shortcomings of conventional therapy

It has been estimated that 10%–20% of patients have severe Crohn's disease that is best treated with anti-TNF therapy, but there has been no systematic evaluation. In population-based studies, 25% of all patients with Crohn's have active disease at any one time (Munkholm et al 1995, 1997), of which 10% will be severe enough to need hospitalization. However, looked at another way, around 50% of all patients with Crohn's disease need surgery, which increases to 80% of those with ileocecal disease (the commonest location) within 15 years of diagnosis. Since surgery will generally only be performed for severe disease not responding to medical therapy, the proportion of patients potentially treated with biologic therapy in the future is likely to be much higher. Even so, there is evidence of under-treatment with biologic agents, especially in Europe (Reddy et al 2005). Alternative treatments are also needed for those who develop immunogenicity on infliximab (estimated at 50% or more, depending on dosing schedule, concomitant therapy, and assay technique) (Vermiere et al 2003). Safety is a crucial factor, with serious or life-threatening adverse events in about 2%–5% of patients given infliximab, double the rate of sepsis in those receiving steroids, and myelotoxicity or risk of lymphoma in those receiving thiopurines (Kandiel et al 2005). Furthermore, there is little evidence that current

therapy changes the natural history or outcome of disease, although some preliminary evidence that early intervention with anti-TNF therapy reduces steroid exposure, reduces hospitalization of surgery in the short term, and promotes mucosal healing (Rutgeerts et al 2004; D'Haens et al 2006; Hommes et al 2006). This sets the scene for further biologic agents, such as certolizumab pegol (CDP870).

Structure, components and activity of certolizumab Fab fragments

Over the last decade there has been increasing interest in the use of antibodies and antibody fragments as therapeutic entities. Antibody molecules have two main functions: to bind to antigen molecules and then to eliminate these from the body. The binding to antigen molecules is facilitated by an antigen-binding domain formed between the heavy- and light-chain variable domains. Within each antibody variable chain there are three regions known as complementary determining regions or CDRs. The space formed by these CDRs enables the antibody molecule to bind its antigen. The interest in the use of antibody fragments, Fab and Fab', is in part due to their reduced size compared with an IgG molecule, which enables them to penetrate more rapidly into body tissues. An additional benefit of these antibody fragments is that they lack an Fc region which fixes complement and can promote undesirable side-effects, such as a cytokine release syndrome (Chapman 2002).

Immunogenicity

Fab fragments are generally less immunogenic than whole antibodies (13), but the concept of immunogenicity needs to be understood, since it is different to antigenicity. Antigenicity simply refers to the process by which an antigen (which can itself be an antibody) binds to a specific receptor and provokes an immune response that may be either *immunogenic* or *tolerogenic*. It is the immunogenic response (*immunogenicity*) that is potentially harmful to the recipient. Humanization of an antibody promotes homology with human proteins, which reduces their antigenic profile, but even human proteins can be immunogenic in humans. Consider the antibodies that develop to recombinant Factor VIII or insulin. Consequently the concept that humanization of its own account reduces immunogenicity is false (Clark 2000). Immunogenicity depends not only on the molecular conformation of the protein, but also on dose, delivery, frequency, concomitant therapy, and individual. The ability

of polyethylene glycol (PEG) to reduce the immunogenicity of foreign proteins has been under investigation, with a view to the production of engineered monoclonal antibodies that are effective but less immunogenic (Clark 2000; Chapman 2002).

Implications of humanization

Humanization is a separate antibody engineering strategy that has tried to tackle the immunogenicity of therapeutic antibodies, but as indicated above is not the whole solution. Humanized antibodies can be generated where the antigen-binding CDRs are murine, while the rest of the antibody, including the antibody variable (V) region framework regions (FRs), is human. The problem is that during the humanization process, the antibody affinity is frequently reduced. This reduction in affinity might be minimized by careful selection of human FRs that are homologous to the original antibody, or by reintroducing the important murine FR residues back into the engineered antibody (Clark 2000). Examples of humanized monoclonal antibodies include visilizumab (antiCD3, Nuvion[®]), trastuzumab (anti-HER-2, Herceptin[®]), and alemtuzumab (antiCD52, Campath[®]).

Mass manufacture

The manufacturing of antibodies and antibody fragments is costly. A potential solution has been to express fragments of antibodies such as Fab' in microbial expression systems such as *Escherichia coli*. This is more economical and yields much higher amounts of protein as a result of large fermenter volumes and shorter fermentation times compared with mammalian cell fermentation. The problem here is that these antibody fragments have very short circulation times in vivo. This in turn can be overcome by conjugation to PEG which results in an increased half-life to proteins to which it is attached, either by avoiding renal clearance since polymer increases the apparent size of the molecule to above the glomerular filtration limit, and/or through evasion of cellular clearance mechanisms (Chapman 2002; National Horizon Scanning Centre 2004). Half-life is increased progressively as the size of PEG is increased; values increase almost 7-fold for a single 25-kDa PEG chain, and 13.5-fold for a single 40-kDa PEG chain (Chapman 2002).

Reducing immunogenicity

The potential benefits of PEGylation are (Chapman 2002):

- 1 Reduced antigenicity and immunogenicity of the molecule to which PEG is attached.

- 2 Improved plasma half-life thereby reducing the requirement for frequent dosing.
- 3 Improved solubility.
- 4 Enhanced proteolytic resistance of the conjugated protein.
- 5 Improved bioavailability via reduced losses at subcutaneous injection sites.
- 6 Reduced toxicity.
- 7 Improved thermal and mechanical stability of the PEGylated molecule.
- 8 Improved formulation into materials used for slow release (depot) administration strategies.

Over the past decade a number of studies have been carried out on PEGylated antibodies and antibody fragments. The known properties of PEG to increase plasma half-life and accumulate in tumours has led to an increased application of PEGylation to antibody fragments such as Fab'. Proven technology for the attachment of PEG site-specifically to antibody fragments, thereby avoiding substantial losses in antigen binding, may quite well lead to further improvement by maintaining binding affinity and homogeneity of product (Chapman 2002). Certolizumab pegol (CDP870) is an example of a PEGylated Fab fragment of a humanized anti-TNF alpha antibody (UCB 2005; National Horizon Scanning Centre 2004) that has been developed for the treatment of Crohn's disease (National Horizon Scanning Centre 2004; Winter et al 2004; Schreiber et al 2005a, 2005b) and rheumatoid arthritis (Choy et al 2002; Keystone et al 2001)

The other way to reduce immunogenicity is concurrent therapy with immunomodulators or pre-treatment with steroids (Baert et al 2003). Whether concomitant immunomodulation is necessary with certolizumab pegol remains to be established. Combination therapy with azathioprine/mercaptopurine or methotrexate is recommended for infliximab, but it is unclear to what extent this changes the risk:benefit ratio (Lichtenstein et al 2006b).

Mechanism of action and pharmacokinetics

Certolizumab pegol has been constructed by grafting the short, hypervariable complementarity-determining regions (CDRs) derived from the murine monoclonal antibody HTNF40 onto an otherwise virtually human immunoglobulin (Ig) Fab' fragment (UCB 2005; National Horizon Scanning Centre 2004; Schreiber et al 2005a). The engineered Fab' fragment retains the biological potency of the original

antibody, but lacks the Fc portion of the parent IgG4 antibody (Winter et al 2004). The Fab' fragment is linked to two cross-linked chains of PEG each of which has a molecular weight of 20 kDa. This site-specific polyethylene glycolation increases the half-life of the antibody fragment to approximately 2 weeks in plasma, thereby increasing the interval between dosing required dosing (Chapman 2002). Certolizumab pegol is administered as a 400-mg subcutaneous injection, initially every 2 weeks for the first three doses and subsequently every 4 weeks for maintenance. Subcutaneous administration of certolizumab pegol has been shown in Phase III trials to be clinically effective with good tolerability in patients with moderate-to-severe Crohn's disease and rheumatoid arthritis. It is possible that the subcutaneous route of drug administration could contribute to the good tolerability because peak serum concentrations are lower than would be achieved after intravenous delivery (National Horizon Scanning Centre 2004; Winter et al 2004; Schreiber et al 2005a, 2005b). Certolizumab pegol is a Fab' fragment that has been designed not to fix complement. It is possible that the absence of the Fc fragment, which is the reason that it does not activate complement-dependent cytotoxicity effector mechanisms, could enhance therapeutic safety and reduce adverse events compared with other anti-TNF agents. This has yet to be established in clinical practice.

Efficacy and safety studies

Effectiveness

Initial studies

A dose-ranging, placebo-controlled, Phase II study evaluated subcutaneous doses of certolizumab pegol 100, 200, or 400 mg against placebo at weeks 0, 4, and 8 in 292 patients with active Crohn's disease (CDAI 220–450 points) (Schreiber et al 2005a). Patients were assessed for efficacy every 2 weeks up to week 12. The primary endpoint was the percentage of patients achieving clinical response at week 12 (a decrease in CDAI of ≥ 100 points) or remission (CDAI ≤ 150 points) in the intention to treat population. Onset of effect of certolizumab pegol was evident at week 2. The percentage of patients achieving response or remission was highest in the certolizumab pegol 400-mg treatment group at all times. The greatest percentage of patients meeting the definition of response or remission was observed at week 10 (certolizumab pegol 400 mg 52.8% vs placebo 30.1%, $p=0.006$). However, at week 12 (the primary endpoint) the difference between the certolizumab pegol- and the placebo-treated groups was not statistically significant (certolizumab pegol 400 mg 44.4% vs placebo 35.6%, $p=0.278$). In a post-

hoc analysis, however, when patients with baseline CRP concentration ≥ 10 mg/L showed clearer separation between active treatment and placebo (week 12, certolizumab pegol 400 mg 53.1% vs placebo 17.9%, $p=0.005$). This effect was achieved almost entirely by reducing the response and remission rates in placebo-treated patients. Health-related quality of life data was also evaluated at weeks 0, 2, 4, 6, 8, 10, and 12 using the Inflammatory Bowel Disease Questionnaire (IBDQ). For all treatment groups, there was an improvement (increase) in IBDQ total scores within 2 weeks of treatment that matched the reduction in CDAI scores. In contrast to the overall CDAI scores, however, there were statistically significant improvements in IBDQ scores for the certolizumab pegol 400-mg group compared with placebo at all time points ($p<0.05$) (Schreiber et al 2005a). Clinically meaningful improvements in IBDQ total score (equivalent to a 16 point increase; Irvine et al 1994) were seen in 52.8% of patients receiving certolizumab pegol 400 mg at week 2, compared with 32.9% in the placebo group. This increased to two thirds (66.7%) at week 12, compared with half (50.7%) in the placebo group (National Horizon Scanning Centre 2004; Schreiber et al 2005a). These data supported the anti-inflammatory effect of certolizumab pegol. In contrast to the certolizumab pegol 400-mg group, clinical response and remission rates in patients receiving certolizumab pegol 200 mg and 100 mg were not generally significantly different from rates in patients receiving placebo, irrespective of baseline CRP concentrations (Schreiber et al 2005a). Certolizumab pegol 400 mg therefore appears to be the optimal dose.

Intravenous administration

In a single-dose, randomized, double blind, placebo-controlled, multicenter, exploratory Phase II trial, certolizumab pegol 1.25, 5, 10, 20 mg/kg, or placebo was administered intravenously to 92 patients with moderate to severe Crohn's disease (CDAI 220–450 points) (Winter et al 2004). Although intended for subcutaneous administration, certolizumab pegol may also be effective for the treatment of Crohn's disease when administered intravenously. By administering certolizumab pegol intravenously, it was possible to explore the use of higher doses than is possible to deliver subcutaneously. The dose 5 mg/kg intravenously is approximately equivalent to a 400-mg subcutaneous dose of certolizumab pegol. The primary endpoint of the study was the percentage of patients achieving clinical response (defined as a decrease in CDAI ≥ 100 points) or remission (CDAI ≤ 150 points) at week 4 in the intention to treat population. A high placebo

response rate of 52%–60% was observed and there were no statistically significant differences in the clinical response rates for any of the certolizumab pegol-treated groups compared with placebo. However, at 2 weeks after infusion, remission was induced in 47.1% of patients administered 10 mg/kg certolizumab pegol, compared with 16% of the placebo group ($p=0.041$). Remission was maintained at week 4, but at week 12 the remission rate was similar to the placebo group (23.5% in the certolizumab pegol 10 mg/kg group vs 32.0% in the placebo group). Interestingly, no additional clinical benefit was observed with the higher dose of certolizumab pegol 20 mg/kg (Winter et al 2004). The possibility that certolizumab pegol is less effective in patients with Crohn's disease when administered as an intravenous infusion rather than subcutaneously cannot be ruled out.

Subsequent studies

The PRECiSE clinical program is composed of 4 Phase III studies (PRECiSE 1, 2, 3, and 4). PRECiSE 1 is a placebo-controlled induction and maintenance study for which there is no comparable trial with infliximab or other anti-TNF agent; PRECiSE 2 is an open-label induction and maintenance study, broadly similar in design to the ACCENT I study; and PRECiSE 3 and 4 are 24-month open label trials assessing the longer-term safety and tolerability of certolizumab, and have yet to report.

PRECiSE 1 randomized 659 patients with moderate to severely active Crohn's disease, to certolizumab pegol 400 mg or placebo at weeks 0, 2, and 4 and then every 4 weeks from week 8 to 24. The co-primary endpoints were response (Δ CDAI >-100 points) at week 6 and at weeks 6 and 26 (Sandborn et al 2006). The overall results showed response at week 6 in 35.2% (certolizumab pegol) vs 26.8% placebo, and at weeks 6 and 26 in 23.1% and 16.0% respectively (all intention to treat, $p \leq 0.05$). Remission rates were significant at week 4 (19.5% vs 11.3%, certolizumab pegol vs placebo $p \leq 0.01$), but not at weeks 6 (21.6% vs 17.2%), or weeks 6 and 26 (14.4% vs 9.8%) respectively. The outcome did not differ if the baseline CRP was >10 mg/L (37.2% vs 26.0% response at week 6, 21.5% vs 12.3% at weeks 6 and 26). In a post-hoc analysis to allow some comparison with the initial placebo-controlled infliximab study in moderate to severe Crohn's disease, the response to a lower standard of efficacy (Δ CDAI ≥ -70 points) at 4 weeks was 44.0% vs 33.7% ($p \leq 0.01$) for certolizumab pegol vs placebo. This indicates that certolizumab pegol is effective at inducing remission in active Crohn's disease.

PRECiSE 2 evaluated the efficacy and tolerability of

subcutaneous certolizumab pegol 400 mg every 4 weeks to maintain clinical response in patients with moderate to severe Crohn's disease after open-label induction (UCB 2005; Schreiber et al 2005b). 668 patients with active Crohn's disease (CDAI 220–450) who had responded to induction therapy with certolizumab pegol 400 mg subcutaneously at week 0, 2, and 4 (decrease in baseline CDAI score ≥ 100 points at week 6), were randomized to maintenance therapy with certolizumab pegol 400 mg or placebo every 4 weeks up to week 24. Patients were stratified according to baseline CRP (CRP <10 mg/L or CRP ≥ 10 mg/L). After open label induction, 64.1% of patients (428 of 668) achieved a clinical response. After the randomized phase at week 26, the clinical response rate in the CRP >10 mg/L was 61.6% for the certolizumab pegol group vs 33.7% for the placebo group ($p < 0.001$). This was no different to the overall response: at the end of 26 weeks clinical response was maintained in 62.8% for certolizumab pegol vs 36.2% for placebo (intention to treat, $p < 0.001$). Furthermore, significantly more of the patients in the certolizumab pegol group were in clinical remission (CDAI <150 points) at 26 weeks compared with placebo (47.9% vs 28.6% respectively, $p < 0.001$) (Schreiber et al 2005b).

Safety

General

All anti-TNF agents have the potential to cause serious or life-threatening events, including sepsis, opportunistic infections, or neoplasia. In a systematic review of pooled data from 9 prospective clinical trials of 3493 patients with rheumatoid arthritis treated with adalimumab or infliximab, the odds ratio (95% confidence interval) for serious infection compared with 1512 controls was 2.0 (1.3–3.1) (Bongartz et al 2006). For certolizumab pegol, the overall incidence and pattern of adverse events reported were comparable across all treatment groups in PRECiSE 1 and 2 and the majority of events were of mild or moderate intensity. The most frequent adverse events included headache, nausea, nasopharyngitis, dizziness, arthralgia, abdominal pain not otherwise specified, and pyrexia.

Serious adverse events

For serious non-Crohn's disease related infections in PRECiSE 2, there were 6/216 (2.8%) in the certolizumab pegol group and 2/212 (0.9%) in the placebo group. This included 1 case of tuberculosis in the certolizumab pegol group and 1 pneumonia (none in placebo). For malignancies, there were 4 malignancies in PRECiSE 1 (in 662 patients)

2 with placebo and 2 with certolizumab pegol, but none in PRECiSE 2 (668 patients) or the dose-ranging study (292 patients). There have been 2 deaths in the three studies (1 each in PRECiSE 1 and 2, neither thought to be associated with certolizumab pegol) (Winter et al 2004; Schreiber et al 2005a, 2005b; Sandborn et al 2006). In both PRECiSE studies, injection site (erythema and pain) adverse events were more common in the placebo-treated patients, while in the dose-ranging 292 patient study, reactions occurred in 2.7%–6.8% of patients for both the placebo and the 400-mg dose. Antinuclear antibodies developed in 8 patients on certolizumab pegol and 2 on placebo, with anti-double stranded DNA antibodies in 1 patient in each group, but were transient (<26 weeks) in all but 2 patients. There were no meaningful effects of certolizumab pegol on hematology and biochemical measurements or urinalysis data.

Comparison with other anti-TNF therapy

It is very difficult to compare these data with those for infliximab or adalimumab, because the patient exposure for infliximab is vastly greater than for certolizumab pegol. Furthermore, concomitant medication, comorbidity, and the source of reporting differ widely. Nevertheless it does appear that certolizumab pegol may be less immunogenic than infliximab. It seems unlikely that it will be associated with a lower risk of sepsis, tuberculosis, or neoplasia, since these are more likely to be generic than drug-specific adverse events.

Patient-specific implications (quality of life, satisfaction, convenience)

Satisfaction

Patient compliance and satisfaction with treatment are important factors in managing chronic conditions, such as Crohn's disease. Evidence is accumulating to show that patient education significantly improves disease outcomes in chronic illness (Moser et al 1995; Caprilli et al 2006). Nonetheless, surveys reveal that patients still feel insufficiently informed and would like greater involvement in their treatment, especially when assessing disease activity, its consequences, and the risks of therapy (Sands et al 2006). It is important to discuss patients' worries and concerns, not only regarding their physical problems but also their emotional needs, which for some will require psychosocial counseling to improve quality of life (Moser et al 1995; Van Der Eijk et al 2004). Changes in disease activity cause

significant psychological distress over time and are closely related to increases and decreases in anxiety and depression scores in IBD patients.

Convenience

The convenience of subcutaneous administration of certolizumab pegol (compared with intravenous infusion with infliximab) will appeal to patients, but is likely to have a major impact only when self-administration becomes possible. At present it needs to be administered by a health care professional, although patients have shown themselves adept at self-administration of more complex interventions (such as immunoglobulin infusions) when trained. There also seems little doubt that the convenience of 4-weekly dosing will appeal compared with daily ingestion of drugs, even though concomitant prescription of immunomodulators will be recommended until there is more clear evidence that this is unnecessary.

Measures of quality of life

Although disease severity indices are traditional outcome measures for trials in Crohn's disease, a major limitation of these indices is that they do not provide a detailed picture of the patient's subjective function, including emotional and social problems associated with IBD. The importance of measuring subjective aspects of health status, referred to as health related quality of life, has become increasingly recognized. Goals of therapy for patients with IBD are to control symptoms, reduce complications, minimize treatment toxicity, and improve quality of life (Mitchell et al 1998; Guyatt et al 1989; Irvine et al 1994; Bernklev et al 2004; Travis et al 2006). Quality of life, a subjective quantitative measure of health perception and function, embraces not only the physical but also emotional and social domains; these are referred to as health-related quality of life (HRQOL). Several different questionnaires are available to measure HRQOL. The Inflammatory Bowel Disease Questionnaire (IBDQ) is the most extensively validated of the quality of life instruments related to IBD with specific questions regarding quality of life in Crohn's disease and ulcerative colitis patients (Guyatt et al 1989). It has been evaluated in clinical trials and observational studies of patients with either Crohn's disease or ulcerative colitis (Mitchell et al 1998; Guyatt et al 1989; Irvine et al 1994; Bernklev et al 2004).

Certolizumab and quality of life

A good understanding of the key predictors of quality of

life and of potential mediating factors will enable better interventions to be implemented to improve the overall quality of life in patients with Crohn's disease. First, priority should be given to develop therapeutic interventions to prevent symptom occurrence and to treat symptoms quickly and effectively when they do arise. Second, new strategies should be developed and deployed to improve the individual's experience of those symptoms that do occur. Certolizumab pegol has been shown to improve quality of life, measured by the Inflammatory Bowel Disease Questionnaire, in Phase II clinical trials (National Horizon Scanning Centre 2004; Schreiber et al 2005a). However, the key test and outcome measure of interest for patients, doctors, health care organizations, and policy makers is the demonstration that biologics such as certolizumab pegol reduce hospitalization, surgery, and time off work. These are robust outcome measures for which there is no comparable substitute; mucosal healing is a potential surrogate marker, but has yet to prove a clear correlation (Rutgeerts et al 2004). It is likely that mucosal healing correlates closely with improvements in quality of life, but this cannot be taken for granted. Reduction in surgery or hospitalization will undoubtedly be associated with improved well being.

Conclusion and place in therapy

The management of inflammatory bowel disease must look at aspects other than drug therapy, dose and timing to achieve its therapeutic goals. The goals are induction of remission, maintenance of remission, limitation of side effects and avoidance of complications.

Certolizumab pegol as a 400-mg subcutaneous injection, initially every 2 weeks for the first 3 doses and subsequently every 4 weeks for maintenance has been shown to be well tolerated and effective. The clinical effect of certolizumab pegol is comparable to infliximab, which is itself comparable to adalimumab (Colombel et al 2006; Hanauer et al 2006; Panaccione et al 2006; Schreiber and Sandborn 2006). It seems probable that all anti-TNF agents will have similar efficacy. The effect of certolizumab pegol is independent of CRP; although it is simply good practice to ensure that active disease is confirmed (by CRP, endoscopy, or other objective measure) before instituting any anti-TNF therapy.

Certolizumab pegol will be indicated for moderately, as well as severely active Crohn's disease (Winter et al 2004; Schreiber et al 2005a, 2005b), but is not yet licensed in Europe or the US (license application submitted to the FDA March 2006). It is not possible to construct an algorithm for treatment, but when compared with infliximab the two

principal advantages are likely to be lower immunogenicity (as shown by anti-drug antibodies, absence of infusion reactions, and low rate of antinuclear antibodies), and the subcutaneous route of administration. These two factors may be sufficient to promote it up the pecking order of anti-TNF agents, but cost will also be a consideration and self-administration has yet to be established. Comparative trials between biologics are desirable. Trials in infliximab-intolerant patients, early treatment strategies, and withdrawal trials to determine the duration of therapy are essential. Essential too is the need to demonstrate an impact on the natural history by showing a reduction in hospitalization and operations for Crohn's disease. This is the acid test of biological therapy.

References

- Alfadhli AA, McDonald JW, Feagan BG. 2003. Methotrexate for induction of remission in refractory Crohn's disease (Cochrane Review). *Cochrane Database Syst Rev*, 1:CD003459.
- Ardizzone S, Bianchi Porro G. 2005. Biologic therapy for inflammatory bowel disease. *Drugs*, 65:2253-86.
- Baert F, Norman M, Vermeire S, et al. 2003. Influence of immunogenicity on the long term efficacy of infliximab in Crohn's disease. *N Engl J Med*, 348:601-8.
- Bernklev T, Jahnsen J, Aadland E, et al. 2004. Health-related quality of life in patients with inflammatory bowel disease five years after the initial diagnosis. *Scand J Gastroenterol*, 39:365-373.
- Bongartz T, Sutton AJ, Sweeting MJ, et al. 2006. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomised controlled trials. *JAMA*, 295:2275-85.
- Caprilli R, Gassull MA, Escher JC, et al. 2006. European Crohn's and Colitis organisation. European evidence based consensus on the management of Crohn's disease: special situations. *Gut*, 55(Suppl 1):i36-58.
- Carter MJ, Lobo AJ, Travis SPL. 2004. Guidelines for the management of inflammatory bowel disease in adults. *Gut*, 53:1-16.
- Chang JT, Lichtenstein GR. 2006. Drug insight: antagonists of tumor-necrosis factor-alpha in the treatment of inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol*, 3:220-8.
- Chapman AP. 2002. PEGylated antibodies and antibody fragments for improved therapy: a review. *Adv Drug Del Rev*, 54:531-45.
- Choy EH, Hazleman B, Smith M, et al. 2002. Efficacy of a novel humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomised, dose-escalating trial. *Rheumatology (Oxford)*, 41:1133-7.
- Clark M. 2000. Antibody humanisation: a case of the "Emperor's new clothes"? *Immunol Today*, 21:397-402.
- Colombel JF, Sandborn WJ, Rutgeerts P, et al. 2006. Adalimumab induces and maintains clinical response and remission in patients with active Crohn's disease: Results of the CHARM trial [abstract]. *Gastroenterology*, DDW:no. 686d.
- D'Haens G, Hommes D, Baert F, et al. 2006. A combination regime of infliximab and azathioprine induces better endoscopic healing than classic step-up therapy in newly diagnosed Crohn's disease [abstract]. *Gastroenterology*, DDW:no. 764.
- Guyatt G, Mitchell A, Irvine EJ, et al. 1989. A New Measure of Health Status for Clinical Trials in Inflammatory Bowel Disease. *Gastroenterology*, 96:804-10.

- Hanauer SB, Feagan BG, Lichtenstein GR, et al. 2002. Maintenance infliximab for Crohn's disease: The ACCENT 1 randomised trial. *Lancet*, 359:1541-9.
- Hanauer S, Sandborn W. 2001. Management of Crohn's disease in adults. *Am J Gastroenterol*, 96:635-43.
- Hanauer SB, Sandborn WJ, Rutgeerts P, et al. 2006. Human anti-tumour necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-1 trial. *Gastroenterology*, 130:323-33, quiz 591.
- Hommes D, Baert F, van Assche G, et al. 2006. The ideal management of Crohn's disease: Top down versus step up strategies, a randomised controlled trial [abstract]. *Gastroenterology*, DDW:no.749.
- Irvine EJ, Feagan B, Rochon J, et al. 1994. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Disease Prevention Trial Study Group. *Gastroenterology*, 106:287-96.
- Ivashkiv LB. 2003. The history, basic science and biology of TNF. *Hospital for special surgery*, September 20.
- Kandiel A, Fraser AG, Korelitz BI, et al. 2005. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut*, 54:1121-5.
- Keystone E, Choy EH, Kalden J, et al. 2001. CDP870, a novel, PEGylated, humanized TNF alpha inhibitor is effective in treating the signs and symptoms of rheumatoid arthritis (RA). Late-breaking abstract No. LB-3, presented at the American College of Rheumatology, 65th Annual Scientific Meeting.
- Korzenik JR. 2006. Investigational therapies in the medical management of Crohn disease. *UpToDate*.
- Lichtenstein GR, Abreu MT, Cohen R, et al. 2006a. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators and infliximab in inflammatory bowel disease. *Gastroenterology*, 130:935-9 and accompanying technical review 940-87.
- Lichtenstein GR, Abreu MT, Cohen R, et al. 2006b. American Gastroenterological Association. American gastroenterological association institute medical position statement on corticosteroids, immunomodulators and infliximab in inflammatory bowel disease. *Gastroenterology*, 130:935-9.
- Loftus EV Jr. 2004. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*, 126:1504-17.
- Mitchell A, Guyatt G, Singer J, et al. 1988. Quality of life in patients with inflammatory bowel disease. *J Clin Gastroenterol*, 10:306-10.
- Moser G, Tillinger W, Sachs G et al. 1995. Disease-related worries and concerns: a study on outpatients with Inflammatory Bowel Disease. *Eur J Gastroenterol Hepatol*, 7:853-8.
- Munkholm P. 1997. Crohn's disease - occurrence and prognosis. An epidemiologic cohort-study. *Dan Med Bull*, 44:287-302.
- Munkholm P, Langholtz E, Davidsen M, et al. 1995. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol*, 30:699-706.
- National Horizon Scanning Centre. 2004. Certolizumab pegol for moderate to severe Crohn's disease. *New and Emerging Technology Briefing*, July.
- National Institute for Clinical Excellence. 2002. Guidance on the use of infliximab for Crohn's disease. Technology Appraisal Guidance No 40. London: National Institute for Clinical Excellence.
- Otley A, Steinhart AH. 2005. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*, 4:CD000296.
- Panaccione R, Hanauer SB, Fedorak R, et al. 2006. Concomitant immunosuppressive and adalimumab therapy in patients with Crohn's disease: 1-year results of the CLASSIC-II study [abstract]. *Gastroenterology*, DDW:no. T1124.
- Pearson DC, May GR, Fick GR, et al. 2000. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev*, 2:CD000067.
- Reddy SI, Friedman S, Telford JI, et al. 2005. Are patients with Inflammatory Bowel Disease receiving optimal care? *Am J Gastroenterol*, 100:1357-1361.
- Rutgeerts P, Van Assche G, Vermeire S. 2004. Optimising anti-TNF treatment in inflammatory bowel disease. *Gastroenterology*, 126:1593-610.
- Sandborn WJ. 2003. Optimizing anti-tumor necrosis factor strategies in inflammatory bowel disease. *Curr Gastroenterol Rep*, 5:501-5.
- Sandborn WJ, Feagan B, Stoinov S, et al. 2006. Certolizumab pegol administered subcutaneously is effective and well tolerated in patients with active Crohn's disease: results from a 26 week placebo-controlled phase III study (PRECISE 1). *Gastroenterology*, 130(Suppl 2):A-107.
- Sandborn WJ, Hanauer SR. 2002. Infliximab in the treatment of Crohn's disease: a user's guide to clinicians. *Am J Gastroenterology*, 97:2962-72.
- Sands BE. 2004a. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology*, 126:1518-32.
- Sands BE. 2004b. Why do anti-tumor necrosis factor antibodies work in Crohn's disease? *Rev Gastroenterol Disord*, 4(Suppl 3):S10-7.
- Sands B, Siegel C, Steve H, et al. 2006. Crohn's disease patients' willingness to accept the risks of serious adverse events in exchange for clinical benefits [abstract]. *Gastroenterology*, DDW:no. W1200.
- Schreiber S, Sandborn WJ. 2006. CLASSIC-1 study, the efficacy of adalimumab. *Gastroenterology*, 130:1929-30.
- Schreiber S, Khaliq-Kareemi M, Lawrance I, et al. 2005b. OP-G-355 Certolizumab Pegol, a humanized anti-TNF PEGylated Fab' fragment, is safe and effective in the maintenance of response and remission following induction in active Crohn's disease: a phase III study (PRECISE). *Gut*, 54(Suppl VII):A82.
- Schreiber S, Rutgeerts P, Fedorak RN, et al; and the CDP870 Crohn's Disease Study Group. 2005a. A randomized, Placebo-controlled trial of Certolizumab Pegol (CDP870) for the treatment of Crohn's disease. *Gastroenterology*, 129:807-18.
- Silverberg MS, Satsangi J, Ahmad T, et al. 2005. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*, 19(Suppl A):5-36.
- Stange EF, Travis SP, Vermeire S, et al. 2006. European Crohn's and Colitis organisation. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut*, 55(Suppl 1):i1-15.
- Su C, Lichtenstein GR, Krok K, et al. 2004. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology*, 126:1257-69.
- Travis S. Advances in therapeutic approaches to ulcerative colitis and Crohn's disease. 2005. *Curr Gastroenterol Rep*, 7:475-84.
- Travis SP, Stange EF, Lemann M, et al; European Crohn's and Colitis organisation. 2006. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut*, 55(Suppl 1):i6-35.
- UCB. 2005. CIMZIA demonstrates significant positive results in its two pivotal phase III Crohn's disease trials [press release]. Accessed 22 November 2006. URL: <http://ir.ucb-group.com/phoenix.zhtml?c=137495&p=irol-newsArticle&ID=735014&highlight=certolizumab>.
- Van Der Eijk I, Verheggen FW, Russel MG, et al. 2004. "Best practice" in Inflammatory Bowel Disease: an international survey and audit. *Eur J Intern Med*, 15:113-120.
- Vermeire S, Noman M, Van Assche G, et al. 2003. Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. *Gastroenterology*, 125:32-9.