Targeting nanomedicines in the treatment of rheumatoid arthritis: focus on certolizumab pegol

Theresa Barnes
Robert Moots

Academic Rheumatology,
University of Liverpool, UK

Abstract: Anti-TNFα therapy has revolutionized the treatment of rheumatoid arthritis (RA) and other inflammatory diseases. These drugs are powerful and expensive. A new anti-TNFα agent, a nanomolecule comprising a humanized Fab' antibody fragment against TNFα with a polyethylene glycol tail, is shortly to complete phase III trials in RA. In this review we will discuss the construct of this new molecule, data from trials so far, and its potential place in the market place.

Keywords: certolizumab pegol, TNFα, rheumatoid arthritis, nanomolecule

Targeting tumour necrosis factor alpha (TNFα) in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease. It is characterized by synovial inflammation, but in addition there are major systemic and extra-articular features. The prevalence of RA is estimated at 1% and it is associated with a high degree of morbidity and significant mortality (Felts and Yelin 1989).

The exact cause of RA has not yet been established, but it appears that in a genetically predisposed person immune system dysregulation drives the development and maintenance of this chronic disease. Over recent years an important role has been identified for the proinflammatory cytokine TNFα in the pathogenesis of RA. Cultured RA synovial cells produce many proinflammatory cytokines. Antibodies against TNFα introduced to these cultures do not only inhibit the activity of TNFα, they also reduce the production of other inflammatory cytokines (IL1, IL6, IL8) (Brennan et al 1989). In this respect, TNFα appears to orchestrate and perpetuate the inflammatory response in RA by increasing proinflammatory cytokines and recruitment of immune cells, stimulating cell proliferation, and mediating the destruction of bone and cartilage (Brennan et al 1989). The concentration of TNFα is elevated in the joints and the blood of patients with RA (Chu et al 1991). Animal models also support a central role for TNFα in inflammatory arthritis (Keffer et al 1991).

Three drugs targeting TNFα are now in common clinical use: infliximab (a chimeric TNFα specific monoclonal antibody with mouse hypervariable domains and human antibody backbone); adalimumab (a recombinant human TNFα specific monoclonal antibody); and etanercept (a fully human construct comprising the p75 TNFα receptor and Fc antibody portion). The efficacy of these agents in controlling the symptoms and signs of RA is further evidence that in many patients with RA TNFα is a central pathogenic mediator.

Correspondence: Robert Moots
Academic Rheumatology,
Clinical Sciences Centre,
University Hospital Aintree,
Longmoor Lane, Liverpool, UK, L9 7AL
Tel +44 151 529 5889
Fax +44 151 529 5888
Email rjmoots@liv.ac.uk

Certolizumab pegol

There are two important regions of antibodies, the Fab and the Fc portions (Figure 1). The Fab portion contains complimentarity-determining regions (CDR), unique sequences of amino acids responsible for binding antigen. The Fc portion is not antigen specific but acts as a backbone and is necessary for other antibody functions including complement fixation and cell lysis. Monoclonal antibodies have a single identical sequence, in contrast to polyclonal antibodies, which have many different sequences and hence antigen-binding properties. The first generation of monoclonal antibodies were generated in mice, but the immunogenicity of murine proteins in humans precluded their use therapeutically, due to their propensity to induce major immune responses (anaphylaxis). Thereafter, strategies have been developed to limit the immunogenicity of monoclonal antibodies. One such strategy is that of "humanization". This involves replacement of murine framework sequences around the CDR with human framework sequences. Certolizumab pegol has been developed using this technique. It consists of only the Fab' portion (50 kD) of a monoclonal antibody directed against TNFα, with humanized framework sequences and a 2x20 kD pegol domain (Figure 2). The resulting molecule contains only the smallest effective antigen-binding part of the monoclonal antibody and is thus referred to as a nanomolecule. The murine part is reduced to a minimum with a parallel reduction in potential for immunogenicity.

Mechanism of action and pharmacokinetics

Certolizumab pegol binds to TNFα and prevents its interaction with specific receptors, hence neutralizing it. Studies have demonstrated that it is more potent at neutralizing membrane-bound TNF than etanercept and more potent at neutralizing soluble TNF than adalimumab and infliximab (Gramlick et al 2006). It lacks an Fc portion and is therefore unable to fix complement or to lyse cells with surface-bound TNFα, in contrast to infliximab and adalimumab (Fossati and Nesbitt 2006a). As it is derived from a monoclonal antibody, certolizumab pegol does not bind lymphotoxin (TNFβ), in contrast to etanercept (Mpofu et al 2005). Certolizumab has also been shown to be the only anti-TNF agent that does not kill activated lymphocytes and monocytes by apoptosis or increase levels of degranulation and necrosis of granulocytes in vitro (Fossati and Nesbitt 2006b). The potential consequences of these structural properties are discussed below.

As a nanomolecule, the Fab' would have a much shorter half-life than other monoclonal antibodies and therefore the disadvantage of requiring a more frequent administration. Therefore the Fab' is bound to a polyethylene glycol moiety (PEG), which increases its half-life and potentially further decreases its immunogenicity. The plasma half-life in humans is 13 days, which is comparable to that of full length humanized antibodies (Baker et al 2006). This allows a once-monthly, subcutaneous dosing regime. This has been confirmed in a phase II study in 36 RA patients (Choy et al 2002).

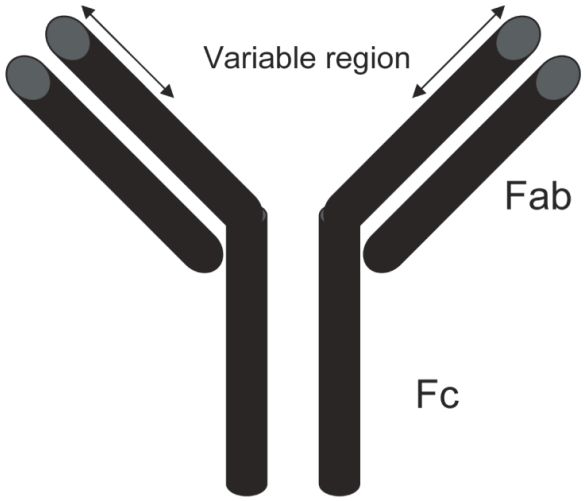

Figure 1 Antibody structure.

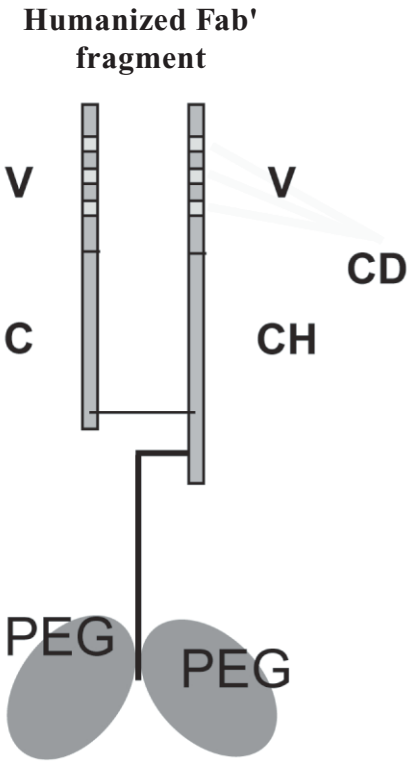

Figure 2 Certolizumab pegol.
Abbreviations: CD, complimentarity domain; C, constant region; CH, constant heavy chain region; PEG, pegol domain; V, variable region.

Efficacy and safety studies

Phase I studies

The results of phase I studies were released in 1999. They demonstrated that therapeutic doses of certolizumab pegol were well tolerated and produced no serious side-effects in healthy volunteers. Both intravenous and subcutaneous administration yielded similar results (Kaushik and Moots 2005).

Phase II studies in RA

The first phase II study was published in 2002. This was a double-blind, randomized, placebo-controlled trial of certolizumab pegol given intravenously as a single infusion at 1, 5, or 20 mg/kg in 36 patients. Patients were included if they had severe active disease as defined as >3 swollen and 6 tender joints and an ESR >29. The response was measured according to the American College of Rheumatology (ACR) response criteria where an ACR20 indicates a 20% clinical improvement from baseline after treatment and an ACR50 and ACR70 indicate a 50% or 70% improvement, respectively. An ACR20 was designed to show difference between drug and placebo, but ACR50 and ACR70 responses are clinically meaningful to patients. The study showed a dose response, with the 1 mg/kg dose being no better than placebo, but significant responses at higher doses. The 20 mg/kg dose showed no clear benefit over the 5 mg/kg dose in the ACR20 response (75% vs 75%, respectively, at 8 weeks), but did show an increase in the number of patients achieving an ACR50 (50% and 12.5%, respectively, at 8 weeks). The treatment was well tolerated, with no infusion-related reactions. There was 1 lower respiratory tract infection in the placebo group and 3 in the treatment groups. These were described as mild to moderate. One severe adverse event was reported. This was an episode of neck pain experienced 3 days after infusion with the lowest dose of 1 mg/kg of certolizumab pegol. An increase in the titre of antinuclear antibodies was seen in 4 patients, 1 in the placebo group and 3 in the treatment groups; however, no change was found in the double stranded DNA titre or anticardiolipin antibodies. There was 1 death in the treatment group, from a pericardial effusion that was not due to infection and was felt by the investigator to be unrelated to the drug (Choy et al 2002).

A second trial was a multicenter, randomized, double-blind, placebo-controlled, dose ranging, phase II study of subcutaneous certolizumab pegol. Patients were given 50, 100, 200, or 400 mg of certolizumab pegol or placebo subcutaneously every 4 weeks for 12 weeks. The response was measured using the ACR criteria outlined above. Again, there was a clear dose response. Patients receiving 400 mg achieved an ACR20 of 60%, ACR50 of 40%, and ACR70 of 29% at 12 weeks. In addition, patients receiving 400 mg also had an improvement in their health-related quality of life. Again the drug was well tolerated (Keystone et al 2001; Pharmacia Corp 2001; Emery et al 2002)

The results of a third trial involving 660 patients were disclosed by Celltech in 2002, showing that patients receiving 400 mg of certolizumab pegol subcutaneously achieved an ACR20 of 75% at 7 days post a single injection (Kaushik and Moots 2005).

Phase III studies in RA

Several phase III trials of certolizumab pegol in RA are underway and complete phase III data are awaited. Trials are exploring the use of certolizumab pegol as a monotherapy and also in combination with methotrexate. Patients recruited had severe active disease with at least 9 tender and swollen joints and either an ESR >30 mm/h or CRP >15 mg/L. Evidence from previous trials using anti-TNF therapies demonstrates that the addition of methotrexate can give additive benefit in patients with RA (Hyrich et al 2006). A press release (UCB Pharma 2004) in September 2004 from Celltech did report positive preliminary results from phase III studies of certolizumab pegol in RA as monotherapy in terms of the primary endpoint (ACR20). Patients receiving the drug had significant ACR20 responses at 1 week, maintained for the duration of the study. In addition they reported similar positive results from the trials assessing combination with methotrexate. Adverse events were similar to those seen in phase I and II studies (UCB Pharma 2004). The delay in publication of phase III studies appears to be for business rather than clinical reasons and the final results are expected in late 2006 or early 2007.

Patient implications

Pegylation reduces immunogenicity by shielding the protein from recognition by the immune system (Mehvar 2000). Because of the pegylated formulation of the nanomolecule certolizumab pegol, immunogenicity of the drug is minimized and half-life increased. This has the dual benefit that the drug can be administered less frequently (monthly) and that it is less likely to induce anti-drug antibody formation than conventional chimeric monoclonal antibodies. Reduced immunogenicity, due to humanization and pegylation, not only means that severe allergic reactions are less likely, but also that the development of neutralizing antibodies may be

reduced. The latter can be responsible for the phenomenon of "dose creep" where the dose of a drug needs to be increased, or the interval between doses decreased, to maintain clinical response. The intravenous dose ranging phase II study revealed that following a single dose of certolizumab pegol no or only low levels of antibodies were identified. Following a second infusion, however, antibodies were detected in all treatment groups (1 mg/kg, 5 mg/kg, 20 mg/kg). Although the incidence of antibodies varied, the trend was for less antibodies with increased dose (Choy et al 2002). The clinical effect of these antibodies will be revealed only by phase III studies, and whether they are neutralizing (and therefore translate into dose creep or late inefficacy) will become fully apparent only with later open label extensions.

The Fab fragment of a monoclonal antibody does not require glycosylation for function and therefore this drug can be produced in *Escherichia coli*, a bacterial host. This makes the production of certolizumab pegol potentially less expensive than existing anti-TNFα therapies. If this were to translate into cheaper drug costs and assuming comparable efficacy and safety to other anti-TNFα agents, there may be pressure from purchasers to favor a less expensive drug, and/or allow treatment of more patients with RA, at earlier stages of disease.

Certolizumab pegol does not have an Fc portion and therefore is not capable of complement fixation or lysis of cells expressing cell surface TNFα. Etanercept is reported to be not capable of complement fixation – a property that has been suggested to underlie its slightly safer profile in relation to the rate of intracellular infections compared with infliximab and adalimumab (Moots et al 2003). A recent study, however, has contradicted this report, showing that etanercept but not certolizumab pegol is capable of complement mediated cell lysis (Fossati and Nesbitt 2006a). It may therefore follow that certolizumab pegol will share this lower rate of intracellular infections (Moots et al 2003). However, as well as neutralizing TNFα, etanercept will also bind to and neutralize a related pro-inflammatory cytokine, lymphotoxin (TNFβ), whereas certolizumab pegol does not. The role of lymphotoxin in RA is not fully known, but in at least one individual, it would appear that neutralizing this cytokine in RA has beneficial effects (Buch et al 2004). Certolizumab pegol is reported not to lyse activated immune cells in vitro. This may have implications for its efficacy in treating inflammatory conditions but equally may make it more specific and therefore reduce the side-effect profile in terms of infection risk. Certainly the reports, quoted above, suggest that unlike other anti-TNFα agents, it does not lead to granulocyte degranulation and necrosis are likely to be positive overall in terms of safety and efficacy.

Conclusions: place in market

Certolizumab pegol is a keenly awaited addition to the family of anti-TNFα agents for the treatment of inflammatory diseases. Although this is already a busy market place, certolizumab pegol has some features that might make it an attractive option: the long half-life allows a fortnightly, subcutaneous drug regime and might even allow monthly drug administration in the future; the lack of complement fixation may impart less risk of intracellular infection than the monoclonal antibody anti-TNFα agents and the potential to be produced more cheaply than other anti-TNFα agents may have a major influence on purchasers.

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