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R E V I E W

Prefilled certolizumab pegol (Cimzia®) syringes for self-use in the treatment of rheumatoid arthritis

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Abstract: A new anti-tumor necrosis factor alpha (TNF-α) inhibitor with a novel mechanism of action has entered phase 3 trials in rheumatoid arthritis (RA). Certolizumab pegol (Cimzia®) is a humanized Fab′ antibody fragment against TNF-α with a polyethylene glycol tail that prevents complement-dependent and antibody-dependent cell-mediated cytotoxicity or apoptosis. Four randomized clinical trials have been published so far. Reported results are similar to those published in previous studies with other TNF-α inhibitors, with ACR20, ACR50, and ACR70 responses of around 60%, 40%, and 20%, respectively, when combined with methotrexate and slightly lower when used as monotherapy. Safety was shown to be similar to that seen with TNF-α blockers and some cases of tuberculosis were seen in the trials, stressing the importance of a complete screening in these patients. Although we still need effectiveness and safety data in larger numbers of patients and longer follow-up, this new TNF inhibitor is a welcome addition to our current armamentarium for the treatment of RA.

Keywords: certolizumab pegol, rheumatoid arthritis therapy, biologic therapies

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with a high degree of morbidity and significant mortality. Although the exact cause of RA has not yet been established, it appears that in a genetically predisposed person, immune system dysregulation drives the development and maintenance of this chronic disease.[1] In recent years, an important role has been identified for the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) in the pathogenesis of RA. TNF-α 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.[1] The concentration of TNF-α is increased in the joints and blood of patients with RA. TNF-α inhibitors revolutionized the management of RA because these agents improve signs and symptoms, physical function, and inhibit structural damage, particularly in combination with methotrexate (MTX).[1–4] TNF-α blockers represent a major advance in RA treatment and are the first choice in biological therapy for patients following an inadequate response to nonbiological disease-modifying antirheumatic drugs (DMARDs).[2,4–7] All 3 TNF-α inhibitors in clinical use (infliximab, adalimumab, and etanercept) have shown similar efficacy in randomized controlled clinical trials. However, individual patient responses to any one or all of these agents vary in clinical practice. Some patients also stop responding to these agents over time or discontinue treatment due to tolerability issues.[8–10]

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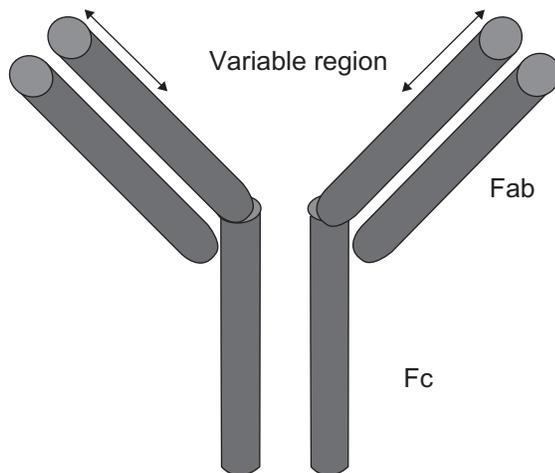Email enrique.soriano@hospitalitaliano.org.ar

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Certolizumab pegol

There are 2 important regions of antibodies, the Fab and Fc portions (Figure 1). The Fab portion contains complimentary-determining regions (CDR), unique sequences of amino acids responsible for binding antigen. The FC portion is not antigen specific but is a necessary backbone for other antibody functions such as complement fixation and cell lysis.[11] Monoclonal antibodies originate from a single cell line and have a single identical sequence. The first generation of monoclonal antibodies was generated in mice, but the immunogenicity of murine proteins in humans makes their use more difficult due to their propensity to induce major immune responses. Therefore, strategies to limit the immunogenicity of monoclonal antibodies such as "humanization" were developed.[11] This involves replacement of murine framework sequences around the CDR with human framework sequences.

Certolizumab pegol (Cimzia®; UCB, lnc.) is a novel TNF inhibitor, consisting of a humanized Fab fragment (50 kD) fused to a 40-kD polyethylene glycol (PEG) moiety (Figure 2).[11] The resulting molecule contains only the smallest effective antigen-binding part of the monoclonal antibody and is thus referred to as a nanomolecule.[11] This unique structure may avoid potential Fc-mediated effects seen *in vitro*, such as complement-dependent or antibody-dependent cell-mediated cytotoxicity or apoptosis.[12] The murine part is reduced to a minimum with a parallel reduction in potential for immunogenicity.[11]

Mechanism of action and pharmacokinetics

Certolizumab pegol binds to TNF-α and prevents its interaction with specific receptors.[11] As mentioned early,

in contrast to infliximab and adalimumab, the lack of an Fc portion prevents the molecule from complement fixation or the lyse of cells with surface-bound TNF-α.[12] Since it is derived from a monoclonal antibody, certolizumab pegol does not bind lymphotoxin (TNF-β),[11] in contrast to etanercept. 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*.[11,12] To prevent a much shorter half-life than other monoclonal antibodies and, therefore, the disadvantage of requiring a more frequent administration, the Fab′ is bound to a PEG moiety, which increases its half-life and potentially further decreases its immunogenicity.[11] The plasma half-life in humans is 13 days, which is comparable to that of the full length humanized antibodies allowing a once monthly, subcutaneous dosing regime.[11]

As this nanomolecule does not require glycosylation for function, this drug can be produced in *Escherichia coli*, a bacterial host.[11] This makes the production of certolizumab pegol potentially less expensive than existing anti-TNF-α therapies.
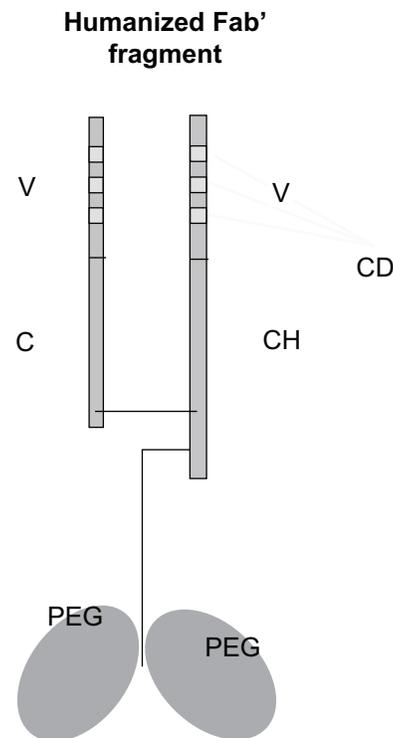

Figure 1 Antibody structure.
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Figure 2 Certolizumab pegol.
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Abbreviations: CD, complimentary domain; C, constant region; CH, constant heavy chain region; PEG, pegol domain; V, variable region.

Efficacy and safety studies

There have been 4 trials published.[13–16] The first was a phase 2 study using intravenous certolizumab as monotherapy.[13] The other 3 used subcutaneous certolizumab, 2 in combination with MTX[15,16] and 1 as monotherapy.[14] No trial included patients with failure to a previous TNF inhibitor (Table 1). Summaries of patients' characteristics and main outcomes are shown in Tables 1 and 2, respectively.

The first phase 2 study was published in 2002.[13] Thirty-six patients were randomized in a double-blind, ascending-dose group study to a single intravenous infusion of placebo (n = 12) or 1, 5, or 20 mg/kg PEGylated humanized anti-TNF fragment (CDP870; each n = 8).[13] Patients were predominantly female (30 of 36) who had a mean age of 56 years and 13 years of RA mean duration. They had received a mean of 5 DMARDs or experimental therapies (with 1 month washout before the beginning of the study) and had active disease (>3 swollen and 6 tender joints and an erythrocyte sedimentation rate [ESR] >28). Continuation of nonsteroidal anti-inflammatory drugs (NSAIDs) and up to 7.5-mg prednisolone daily was allowed. Following the blinded dosing period, 32 patients received a single open-label infusion of either 5-mg/kg CDP870 or 20-mg/kg CDP870. In the blinded dosing period, 6 of 12 placebo patients withdrew from the study (for deterioring RA < 4 weeks after dosing). Two of 24 CDP870-treated patients withdrew, both in the 1-mg/kg group (for deterioring RA or lost to follow-up >4 weeks after dosing). 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. 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 it did show an increase in the number of patients achieving an ACR50 (50% and 12.5%, respectively, at 8 weeks). Following the open-label dose of CDP870, similar beneficial effects were achieved. The treatment was well tolerated with no infusion-related reactions. The commonest adverse event (AE) was headache. There was 1 lower respiratory tract infection in the placebo group and 3 in the treatment groups. These were described as mild to moderate. Three patients developed a urinary tract infection 1–2 months after CDP870 treatment. One severe AE 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.[13] An increase in antinuclear antibody was seen in 4 patients (1 in the placebo group and 3 in the treatment groups); no change was found in anti-DNA or anticardiolipin antibodies. In the open phase, 1 patient who received 20 mg/kg died from complications following rapid drainage of a large, chronic rheumatoid pericardial effusion.[13] No infective agent was isolated from either the pericardial fluid or peripheral blood. In the opinion of the investigator, this event was unrelated to treatment with CDP870.

Table 1 Baseline demographic and patients' characteristics in different trials in patients receiving certolizumab pegol

	Efficacy of CDP870[13] (20/mg/kg; n = 8)	RAPID 1[15] (400 mg; n = 390)	RAPID 2[16] (400 mg; n = 246)	FAST4WARD[14] (400 mg; n = 111)
Mean age (SD)	51 (8)	52.4 (11.7)	51.9 (11.8)	52.7 (12.7)
Sex, n female (%)	6 (75)	326 (83.6)	192 (78)	87 (78.4)
Disease duration (y), mean (SD)	14 (13)	6.2 (4.4)	6.5 (4.3)	8.7 (8.2)
Rheumatoid factor-positive, n (%)	4 (50)	326 (83.6)	179 (75.5)	110 (100)
No. of previous DMARDs, mean (SD)	4 (2)	1.3 (1.3)[a]	1.3 (1.2)[a]	2 (1.2)
Previous anti-TNF use, n (%)	0	0	2 (0.8)	0
No. of tender joints, mean (SD)	NR	31.1 (13.3)	30 (13.9)	29.6 (13.7)
No. of swollen joints, mean (SD)	NR	21.5 (9.8)	21 (10.2)	21.2 (10.1)
HAQ DI, mean (SD)	NR	1.7 (0.6)	1.6 (0.6)	1.4 (0.63)
DAS28, mean (SD)	6.2	6.9 (4.8–9.1)[b]	6.8 (0.79)	6.3 (1.1)

Notes: [a]Excluding MTX; [b]Median (minimum–maximum).
Abbreviations: SD, standard deviation; NR, not reported.

Table 2 Efficacy of certolizumab pegol vs placebo in different randomized controlled trials

Study, type (reference)	Number of patients; active, placebo	Time to final assessment, wk	% ACR20 response, active vs placebo	% ACR50 response, active vs placebo	% ACR70 response, active vs placebo
Efficacy of CDP870, phase 2[13]	8 (20 mg/kg; IV), 12	8	75 vs 16.7	50 vs 0	NR
RAPID 1, phase 3[15]	390 (400 mg; SC), 199	24	61 vs 14	40 vs 8	21 vs 3
RAPID 2, phase 3[16]	246 (400 mg; SC), 127	24	58 vs 9	33 vs 3	11 vs 1
FAST4WARD, phase 3[14]	111 (400 mg; SC), 109	24	45.5 vs 9	23 vs 4	5.5 vs 0

Abbreviations: NR, not reported; IV, intravenous infusion; SC, subcutaneous.

This study confirmed that CDP870 reduced inflammation and improved symptoms in RA.[13] Clinical improvement, as measured by the ACR20 response criteria, in the 5-mg/kg group and 20-mg/kg group (75% and 75%, respectively), was comparable with that of previously reported with etanercept (60%)[7] and infliximab (60%).[2]

The second trial was RA Prevention of Structural Damage 1 (RAPID 1) trial. The aim of this study was to evaluate the efficacy and safety of 2 dosage regimens of subcutaneous lyophilized certolizumab pegol in patients with active RA with an inadequate response to MTX therapy alone.[15] Primary end points were the ACR20 response rate at week 24 and the mean change from baseline in the modified total sharp score (mTSS) at week 52.

The study was conducted at 147 centers worldwide between February 2005 and October 2006.[15] In this 52-week, phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, 982 patients were randomized 2:2:1 to receive treatment with subcutaneous certolizumab pegol at an initial dosage of 400 mg given at weeks 0, 2, and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus MTX, or placebo plus MTX. Concomitant treatment with oral corticosteroids (10 mg/day of prednisone or equivalent with a stable dosage for 4 weeks prior to baseline and continuing throughout the study), NSAIDs/cyclooxygenase-2 inhibitors, and analgesics were allowed. Parenteral corticosteroids were not permitted. DMARDs (exclusive of MTX) had to be discontinued 28 days prior to baseline, except for leflunomide, which had to be discontinued 6 months prior to baseline unless a cholestyramine washout was performed.

At week 24, ACR20 response rates for the certolizumab pegol 200-mg group and 400-mg group were 58.8% and 60.8%, respectively, as compared with 13.6% for the placebo group.[15] The onset of action of certolizumab pegol was evident after the first injection. Differences in ACR20 response rates vs placebo were significant at week 1 and were sustained at week 52 ($P < 0.001$). Maximum ACR50 and

ACR70 response rates in the group taking 200 mg of certolizumab pegol were achieved by weeks 14–20 of treatment. At week 52, mean radiographic progression from baseline was reduced in patients treated with certolizumab pegol 200 mg (0.4 sharp units) or 400 mg (0.2 sharp units) as compared with that in placebo-treated patients (2.8 sharp units; $P < 0.001$). Improvements in all ACR core set of disease activity measures, including physical function, were observed by week 1 with both certolizumab pegol dosage regimens. Most AEs were mild or moderate (including susceptibility to infection: lower respiratory tract infection, urinary tract infection, gastroenteritis, and tuberculosis).[15] A total of 5 patients developed tuberculosis after 1.5–9 months of treatment in active drug groups. The occurrence of tuberculosis was mainly in purified protein derivative (PPD)-positive individuals (3 of 5) living in Eastern Europe, where the prevalence of latent tuberculosis is particularly high.[15]

This study concluded that treatment with certolizumab pegol 200 or 400 mg plus MTX resulted in a rapid and sustained reduction in RA signs and symptoms, inhibited the progression of structural joint damage, and improved physical function as compared with placebo plus MTX treatment in RA patients with an incomplete response to MTX.

The third trial was efficacy and safety of certolizumab pegol plus MTX in active RA: the RAPID 2 study.[16] The objective of this study was to evaluate the efficacy and safety of certolizumab pegol vs placebo, plus MTX, in patients with active RA. The primary end point was ACR20 response at week 24. Secondary end points included ACR50 and ACR70 responses, change from baseline in mTSS, ACR core set variables and physical function.

This was an international, multicenter, phase 3, randomized, double-blind, placebo-controlled study at 76 international sites (June 2005 to September 2006) in active adult-onset RA. A total of 619 patients were randomized 2:2:1 to subcutaneous certolizumab pegol (liquid formulation) 400 mg at weeks 0, 2, and 4 followed by 200 mg, or 400 mg plus MTX, or placebo plus MTX, every 2 weeks for 24 weeks. Oral corti-

costeroids (10 mg/day prednisone equivalent) and NSAIDs and cyclooxygenase-2 inhibitors were permitted provided that the doses were stable within 28 and 14 days of baseline, respectively, and remained stable during the study.[16]

Only 17 (13.4%) placebo patients completed the study vs 174 (70.7%) and 181 (73.6%) in the certolizumab pegol 200-mg group and 400-mg group, respectively. More placebo-treated patients (79.5%; n = 101) discontinued treatment owing to lack of ACR20 response at week 16 vs certolizumab pegol 200 mg (19.9%; n = 49) and 400 mg (18.7%; n = 46). Certolizumab pegol conferred rapid improvement in the signs and symptoms of RA. Significantly higher ACR20 responses were seen with certolizumab pegol as early as week 1, increased over the first 12 weeks and were maintained through week 24. A significant proportion of the total effect of certolizumab pegol was seen by week 4. ACR20 response rates were 57.3% and 57.6% for patients in the certolizumab pegol 200-mg group and 400-mg group, respectively, vs 8.7% for the placebo group ($P \leq 0.001$); certolizumab pegol 200 and 400 mg also significantly inhibited radiographic progression; mean changes from baseline in mTSS at week 24 were 0.2 and 0.4, respectively, vs 1.2 for placebo ($P \leq 0.01$). For patients who withdrew at week 16, there was significantly less radiographic progression in certolizumab pegol-treated patients (combined data) than with placebo. Certolizumab pegol-treated patients reported rapid and significant improvements in physical function vs placebo; mean changes from baseline in HAQ-DI at week 24 were 20.50 and 20.50, respectively, vs 20.14 for placebo ($P \leq 0.001$).[16] Most AEs were mild or moderate with low incidence of withdrawals due to them. An isolated increase in activated partial thromboplastin time was seen for patients treated with certolizumab pegol and placebo in this study. However, no association was seen between increased coagulation assay time and bleeding events. Serious infections, including tuberculosis, were reported more frequently with certolizumab pegol than placebo, consistent with rates associated with other anti-TNF treatments.[17] As seen in RAPID 1 trial, 5 cases of tuberculosis in active arms were reported. Again all cases were from Eastern Europe and 2 of 5 cases had a positive PPD test. If current screening criteria would have been used 2 of these patients would have been excluded from the study, but not the other 3.

This study demonstrated that the efficacy and safety of certolizumab pegol in the short term is consistent with previously published results for other anti-TNF therapies.[2–4]

Interestingly, the data shown in the RAPID 1 and RAPID 2 studies are evidence towards the fact that the Fc portion, which is lacking in certolizumab pegol, is not necessary for TNF inhibitors to be clinically effective in RA. Thus, the primary mode of action of TNF inhibitors in RA does not appear to involve Fc-mediated effects but rather the binding and inactivation of TNF and, probably, reverse signaling, which can also be mediated by an Fc-free Fab′ molecule such as certolizumab pegol.[16–18]

The last trial published was efficacy and safety of certolizumab pegol monotherapy in patients with active RA: the FAST4WARD (eFficAcy and Safety of cerTolizumab pegol – 4 Weekly dosAge in RheumatoiD arthritis) study.[14] In this 24-week, multicenter, randomized, double-blind, placebo-controlled study, 220 patients previously failing > 1 DMARD were randomized 1:1 to receive lyophilized subcutaneous certolizumab pegol 400 mg (n = 111) or placebo (n = 109) every 4 weeks. The primary end point was ACR20 improvement at week 24.[14] Secondary end points included ACR50/70 response, ACR component scores, 28-joint Disease Activity Score Erythrocyte Sedimentation Rate 3 (DAS28(ESR)3), patient-reported outcomes (including physical function, health-related quality of life, pain, and fatigue), and safety.

At week 24, the ACR20 response rates were 45.5% for certolizumab pegol 400 mg every 4 weeks vs 9.3% for placebo ($P < 0.001$). Differences for certolizumab pegol vs placebo in the ACR20 response were statistically significant as early as week 1 through week 24 ($P < 0.001$). Significantly fewer patients on certolizumab pegol (21.6%) withdrew due to lack of efficacy compared with placebo (68.8%). Significant improvements in ACR50, ACR components, DAS28(ESR)3 and all patient-reported outcomes were also observed early with certolizumab pegol and were sustained throughout the study.[14] Certolizumab pegol was associated with a low incidence of discontinuation due to AEs (4.5%). The rate of serious infections was 1.8% for certolizumab pegol vs 0% for placebo. There were no reports of tuberculosis, opportunistic infections, malignancy (including lymphoma), demyelinating disease, or congestive heart failure in either group. The incidence of injection site reactions (4.5%) was low with certolizumab pegol; the incidence of injection site pain (0%) was also low when compared with placebo. Overall, within the limited of duration of exposure, the AE profile for certolizumab pegol was consistent with other TNF-α inhibitors. Nine (8.1%) patients developed neutralizing antibodies to certolizumab pegol. No autoimmune clinical manifestations (eg, lupus-like syndrome) were observed.

The authors concluded that treatment with certolizumab pegol 400-mg monotherapy every 4 weeks effectively reduced the signs and symptoms of active RA in patients previously failing >1 DMARD compared with placebo, and demonstrated an acceptable safety profile.

Recently, the impact of certolizumab pegol in combination with MTX on productivity using the RA-specific Work Productivity Survey was assessed in patients included in RAPID 1 and RAPID 2 trials.[19] Certolizumab significantly reduced work absenteeism and presenteeism among patients working outside the home.[19] Significant reductions in number of household days lost, household days with productivity reduced by ≥50%, and days lost due to RA for participation in family, social, and leisure activities were also noted in patients in active treatment.[19] These results would be relevant, as reductions in indirect costs are important when considering cost effectiveness analysis.

Certolizumab has also been used with success in Crohn's disease.[20–23] Three trials and a meta-analysis enrolling a total of 1,040 patients have been published.[20–23] Certolizumab was effective for rapid induction and long-term maintenance of clinical response or remission and improved quality of life in patients with Crohn's disease. Certolizumab was also effective for patients who have lost response to infliximab.[24] Reinduction with certolizumab in patients who have flared on maintenance therapy was useful to rescue a significant proportion of patients.[25]

Conclusions

This new TNF inhibitor has shown a similar efficacy when compared with existing TNF blockers, either in combination with MTX or as monotherapy. The question is whether in a market with many options for TNF blockage there is place for a new TNF inhibitor. In that sense, certolizumab pegol has some features that might make it an attractive option: a long half-life that allows a fortnightly, subcutaneous drug regime and might even allow monthly drug administration in the future and the lack of complement fixation may impart less risk of intracellular infection than the monoclonal antibody anti-TNF-α agents. Finally, the potential to be produced less expensively than other anti-TNF-α agents plus the positive influence on absenteeism and presenteeism may have a major influence on purchasers[11] and cost effectiveness analysis. The reduction of infection has not been proven yet, and in fact too many cases of tuberculosis were seen in RAPID 1 and RAPID 2 trials, although to some extent explained by lack of stringency in exclusion criteria.

The other major problem with certolizumab pegol is that we do not have long-term studies, nor do we have data of safety and effectiveness from biologic registries. Finally, there is still no evidence that certolizumab pegol is useful in patients failing other TNF blockers.

In summary, certolizumab pegol is a promising TNF inhibitor with a novel mode of action, although long-term effect and safety issues are still pending.

Until not long ago, therapeutic options for patients with RA were not only limited but also of little efficacy. New options are very much welcomed by rheumatologists and patients alike.

Disclosure

The authors report no conflicts of interest in this work.

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