Certolizumab pegol for the treatment of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the joints. The cause of RA is unknown. TNF plays a pivotal role in the pathogenesis of RA. Since the late 1990s, the development of biologic agents that target TNF-α has revolutionized the approach to treating RA. Five inhibitors of TNF-α are currently available for clinical use. Certolizumab pegol is a novel TNF-α inhibitor, consisting of a humanized Fab fragment fused to a 40 KDa polyethylene glycol moiety. After a loading dose of 400 mg at weeks 0, 2 and 4, the drug is administered as maintenance therapy at 4-week intervals by subcutaneous injection. It is demonstrated that it improves the signs and symptoms of disease, quality of life and slows the progressive destruction of joints. Certolizumab pegol was generally well tolerated when used as a monotherapy or in combination with methotrexate, with most adverse events being of mild-to-moderate intensity, with a response rate similar to that of other biological therapy available for the treatment of RA. In conclusion, certolizumab pegol is an effective new option for the treatment of RA.

KEYWORDS: certolizumab pegol  rheumatoid arthritis  TNF-α inhibitors

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the joints. If left untreated it leads to joint destruction and severe disability. It affects 0.5–1% of the population in Western countries and has an annual incidence estimated to be approximately 30 per 100,000 population. The disease prevalence is approximately 1% in Caucasians, but varies between 0.1% (in rural Africans) and 5% (in Pima, Blackfeet and Chippewa Indians). Women are affected two- to three-times more often than men [1].

The cause of RA is not known, but many possible etiologies have been identified [101]. Multiple different factors probably interact in genetically susceptible hosts to initiate polyarticular synovitis [2–8]. Once started, the process ultimately becomes self-perpetuating. However, it is known that the inflammation and joint damage is mediated by an imbalance between anti-inflammatory and proinflammatory cytokines, such as TNF-α, IL-1 and IL-6 [9–11].

Since the late 1990s the development of biologic agents that target cytokines involved in the inflammation cascade (particularly TNF-α inhibitors) has revolutionized the approach to treating RA.

A total of four biologic therapies based on different immunopathogenetic mechanisms have achieved major impact in RA:

- TNF-α inhibition [12–14];
- B-cell depletion [15];
- Disruption of T-cell costimulation (anti-CD28 therapy) [16];
- IL-1 and -6 receptor inhibition [17].

Clinical guidelines from the American College of Rheumatology (ACR) recommend that these therapies are used in combination with methotrexate (MTX) in patients with early RA who have not previously received disease modifying antirheumatic drugs (DMARDs) and who have high disease activity and features of a poor prognosis, and in patients who have had an inadequate response to nonbiologic DMARDs including MTX [18].

Overview of the market

A total of five inhibitors of TNF-α are available for clinical use: etanercept, infliximab, adalimumab and, recently, golimumab and certolizumab pegol (CZP) (Figure 1).

Although they have not been compared in head-to-head trials, all of them have shown similar efficacy in randomized, controlled clinical trials in RA as monotherapy or, more effectively, in combination with MTX (Table 1).

Etanercept is a recombinant fusion protein that consists of the soluble TNF receptor (p75) linked to the Fc portion of human IgG1
Certolizumab pegol for the treatment of rheumatoid arthritis

**Drug Evaluation**

Modesto, Spinello, Nicchi & Cottone

Certolizumab pegol (Cimzia®, UCB Pharma) is a novel PEGylated, Fc-free, TNF-α inhibitor recently approved for the treatment of RA.

Chemistry

Certolizumab pegol is a TNF-α inhibitor, consisting of a humanized Fab fragment fused to a 40 KDa polyethylene glycol (PEG) moiety. It neutralizes membrane-associated and soluble TNF-α. The lack of the Fc region may avoid potential Fc-mediated effects such as complement or antibody-dependent, cell-mediated toxicity, which have been observed in vitro; attachment of the PEG moiety to the Fab fragment increases the plasma half-life to approximately 2 weeks, allowing of these were statistically better than placebo in achieving ACR50; only anakinra showed no difference than placebo.

The indirect comparison using a hierarchical linear mixed model demonstrated similar efficacy for the primary efficacy outcome for all biologics. The only exception was for anakinra, which was less efficacious than etanercept, rituximab and adalimumab. Similar results were also observed for safety.

The main safety outcome was withdrawals due to adverse events: abatacept, etanercept and rituximab did not differ significantly from placebo in withdrawals due to adverse events; for adalimumab, anakinra and infliximab, withdrawals due to adverse events were higher in the treatment arm than in the placebo group.

No difference was observed in people who withdrew from the study because of side effects with etanercept, rituximab and abatacept.

In 2008, a meta-analysis of efficacy and safety of all anti-TNF-α available drugs (etanercept, adalimumab and infliximab) was published [23]. The conclusion was that anti-TNF-α inhibition was an efficacious treatment with similar results irrespective of the administered drugs. The only variable influencing the response to treatment was the prior response to DMARD treatment.

The safety profile was also comparable for all the drugs, even if for etanercept it was a little superior with a smaller proportion of patients withdrawing from the trial because of adverse events.

Furthermore, the authors did not find a significant difference in the development of malignancies during the follow-up times in the studies comparing the group of patients treated with anti-TNF-α with the placebo group.

**Introduction to the compound**

Certolizumab pegol (Cimzia®, UCB Pharma) is a novel PEGylated, Fc-free, TNF-α inhibitor recently approved for the treatment of RA.

Figure 1. Molecular structures of TNF antagonists.

CDR: Complementarity-determining region; PEG: Polyethylene glycol; TNFR: Tumor necrosis factor receptor.
Table 1. Efficacy of anti-TNF-α drugs on ACR50 response.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Trial</th>
<th>Groups</th>
<th>Number of patients</th>
<th>ACR50 6 month</th>
<th>ACR50 12 month</th>
<th>ACR50 24 month</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipsky et al. (2000)</td>
<td>IFX + MTX vs MTX</td>
<td>3 mg/kg 8 weeks + MTX 3 mg/kg 4 weeks + MTX 10 mg/kg 4 weeks + MTX 10 mg/kg 4 weeks + MTX Total IFX MTX Total</td>
<td>86 86 87 81 340 88 428</td>
<td>22/86 25/86 27/87 21/81 95/340 4/88</td>
<td>18/86 29/86 34/87 31/81 112/340 7/88</td>
<td>NA [42]</td>
<td></td>
</tr>
<tr>
<td>St Clair et al. (2004)</td>
<td>IFX + MTX vs MTX</td>
<td>3 mg/kg 8 weeks + MTX 6 mg/kg 8 weeks + MTX Total IFX MTX Total</td>
<td>373 751 738 298 1049</td>
<td>NA</td>
<td>NA</td>
<td>171/373 189/378 360/751 161/298</td>
<td>NA [43]</td>
</tr>
<tr>
<td>Quinn et al. (2005)</td>
<td>IFX + MTX vs MTX</td>
<td>3 mg/kg 8 weeks + MTX MTX total</td>
<td>10 10 20</td>
<td>NA</td>
<td>08/10</td>
<td>4/10</td>
<td>NA [44]</td>
</tr>
<tr>
<td>Westhovens et al. (2006)</td>
<td>IFX + MTX vs MTX</td>
<td>3 mg/kg 8 weeks + MTX 10 mg/kg 8 weeks + MTX Total IFX MTX Total</td>
<td>360 721 361 363 1084</td>
<td>110/360 119/361 229/721 33/363</td>
<td>NA</td>
<td>NA</td>
<td>NA [45]</td>
</tr>
<tr>
<td>Moreland et al. (1999)</td>
<td>ETN vs placebo</td>
<td>25 mg twice weekly 10 mg twice weekly Total ETN Placebo Total</td>
<td>78 154 76 80 234</td>
<td>31/78 18/76 49/154 4/80</td>
<td>NA</td>
<td>NA</td>
<td>NA [46]</td>
</tr>
<tr>
<td>Weinblatt et al. (1999)</td>
<td>ETN + MTX vs MTX</td>
<td>25 mg + MTX MTX total</td>
<td>59 30 89</td>
<td>23/59</td>
<td>1/30</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bathon et al. (2000)</td>
<td>ETN vs MTX</td>
<td>25 mg twice weekly 10 mg twice weekly Total ETN MTX Total</td>
<td>207 233 208 415 217 632</td>
<td>NA</td>
<td>NA</td>
<td>101/207 93/217</td>
<td>NA [48]</td>
</tr>
<tr>
<td>Van der Heijde et al. (2006)</td>
<td>ETN + MTX vs ETN vs MTX</td>
<td>25 mg twice weekly + MTX 25 mg twice weekly Total ETN MTX Total</td>
<td>231 223 222 454 228 682</td>
<td>NA</td>
<td>NA</td>
<td>159/231 107/223 266/454 98/228 164/231 284/454 96/228</td>
<td>NA [49]</td>
</tr>
<tr>
<td>Weinblatt et al. (2003)</td>
<td>ARMADA ADA + MTX vs MTX</td>
<td>40 mg/2 weeks + MTX 20 mg/2 weeks + MTX 80 mg/2 weeks + MTX Total ADA MTX Total</td>
<td>67 69 73 209 228 627 682</td>
<td>37/67 22/69 31/73 90/209 5/62</td>
<td>NA</td>
<td>NA</td>
<td>NA [50]</td>
</tr>
<tr>
<td>van de Putte et al. (2004)</td>
<td>ADA vs placebo</td>
<td>40 mg/2 weeks 20 mg/2 weeks 40 mg/week Total ADA Placebo Total</td>
<td>113 136 112 111 434 110 554</td>
<td>25/113 20/106 23/112 36/103 104/434 9/110</td>
<td>NA</td>
<td>NA</td>
<td>NA [51]</td>
</tr>
<tr>
<td>Furst et al. (2003)</td>
<td>STAR ADA + DMARDs vs DMARDs</td>
<td>40 mg/2 weeks DMARD Total</td>
<td>318 318 318 636</td>
<td>93/318</td>
<td>35/318</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ACR50: 50% improvement in the American College of Rheumatology Symptomatic Criteria; ADA: Adalimumab; CZP: Certolizumab pegol; DMARD: Disease modifying anti-rheumatic drug; ETN: Etanercept; GLM: Golimumab; IFX: Infliximab; MTX: Methotrexate; NA: not applicable.
dosing every 2 or 4 weeks (minimum 2 weeks). In addition, PEylation may result in decreased immunogenicity and proteolysis [26–31,102].

**Pharmacodynamics**

Certolizumab pegol binds to human TNF-α with high affinity neutralizing both soluble and membrane bound TNF-α, without neutralizing TNF-β [29–31]. Certolizumab, unlike infliximab, adalimumab and etanercept, does not mediate cell-dependent and antibody-dependent cell-mediated cytotoxicity and does not cause apoptosis of peripheral blood lymphocytes or monocytes [26,29,31]. Certolizumab demonstrated greater potency than adalimumab and infliximab in neutralizing signaling induced by soluble TNF-α, and similar potency to that of etanercept. It neutralizes membrane anti-TNF-α (mTNF) in a dose-dependent manner; it has similar potency to that of adalimumab and infliximab in neutralizing mTNF mediated effects and greater potency than etanercept [26,29,31]. It also inhibits IL-1β production and lipopolysaccharide-induced TNF-α in a dose-dependent manner; it also causes a significant decrease of C-reactive protein levels [102].

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**Table 1. Efficacy of anti-TNF-α drugs on ACR50 response.**

<table>
<thead>
<tr>
<th>Author (year)</th>
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<th>Number of patients</th>
<th>ACR50 6 month</th>
<th>ACR50 12 month</th>
<th>ACR50 24 month</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keystone et al. (2004)</td>
<td>ADA + MTX vs MTX</td>
<td>40 mg/2 weeks + MTX, 20 mg/week + MTX, Total ADA, MTX, Total</td>
<td>207 (212)</td>
<td>80 (87)</td>
<td>167 (192)</td>
<td>NA</td>
<td>[53]</td>
</tr>
<tr>
<td>Breedveld et al. (2006)</td>
<td>PREMIER ADA + MTX vs ADA vs MTX</td>
<td>40 mg/2 weeks + MTX, 40 mg/2 weekS, Total ADA, MTX, Total</td>
<td>268 (274)</td>
<td>257 (278)</td>
<td>NA</td>
<td>158 (166)</td>
<td>[54]</td>
</tr>
<tr>
<td>Keystone et al. (2008)</td>
<td>RAPID 1 CZP + MTX vs MTX</td>
<td>CZP 200 mg/2 weeks + MTX, CZP 400 mg/2 weeks + MTX, Total CZP, MTX + placebo, Total</td>
<td>393 (390)</td>
<td>145 (155)</td>
<td>NA</td>
<td>NA</td>
<td>[33]</td>
</tr>
<tr>
<td>Smolen et al. (2009)</td>
<td>RAPID 2 CZP + MTX vs MTX</td>
<td>CZP 200 mg/2 weeks + MTX, CZP 400 mg/2 weeks + MTX, Total CZP, MTX + placebo, Total</td>
<td>246 (246)</td>
<td>80 (81)</td>
<td>NA</td>
<td>NA</td>
<td>[34]</td>
</tr>
<tr>
<td>Fleischmann et al. (2009)</td>
<td>FAST4WARD CZP vs MTX</td>
<td>CZP 400 mg/4 weeks, Placebo</td>
<td>111 (109)</td>
<td>25 (25)</td>
<td>NA</td>
<td>NA</td>
<td>[35]</td>
</tr>
<tr>
<td>Fleischmann et al. (2008)</td>
<td>GO-BEFORE GLM + MTX vs GLM vs MTX</td>
<td>GLM 100 mg/4 weeks, GLM 100 mg/4 weeks + MTX, Total GLM, MTX, Total</td>
<td>159 (159)</td>
<td>52 (58)</td>
<td>NA</td>
<td>NA</td>
<td>[55]</td>
</tr>
<tr>
<td>Keystone et al. (2009)</td>
<td>GO-FORWARD GLM + MTX vs GLM vs MTX</td>
<td>GLM 100 mg/4 weeks, GLM 100 mg/4 weeks + MTX, Total GLM, MTX, Total</td>
<td>133 (133)</td>
<td>26 (43)</td>
<td>NA</td>
<td>NA</td>
<td>[56]</td>
</tr>
<tr>
<td>GO AFTER (2009)</td>
<td>GLM vs Placebo</td>
<td>GLM 50 mg/4 weeks, GLM 100 mg/4 weeks, Total GLM, Placebo, Total</td>
<td>153 (153)</td>
<td>28 (31)</td>
<td>NA</td>
<td>NA</td>
<td>[57]</td>
</tr>
</tbody>
</table>

**ACR50:** 50% improvement in the American College of Rheumatology Symptomatic Criteria; ADA: Adalimumab; CZP: Certolizumab pegol; DMARD: Disease modifying antirheumatic drug; ETN: Etanercept; GLM: Golimumab; IFX: Infliximab; MTX: Methotrexate; NA: not applicable.
In the placebo-controlled trials [32–35] in patients with RA receiving CZP alone or in association with MTX, the incidence of antibodies to CZP was 7%; in the subgroup analysis, patients treated with CZP plus MTX had a lower rate of neutralizing antibodies than patients treated with CZP alone (2 vs 8%); the presence of antibodies was associated with reduced efficacy.

**Pharmacokinetics & metabolism**

Pharmacokinetic data was derived from studies in healthy subjects who received subcutaneous (up to 800 mg) or intravenous (up to 10 mg/kg) CZP [36].

Single subcutaneous or intravenous doses of CZP have predictable dose-related plasma concentration with a linear relationship between the dose administered and the Cmax. In multiple dose studies, following the loading dosage there was a Cmax of 39–43 µg/ml at week 5 [102]. The Cmax was achieved between 54 and 171 h after subcutaneous administration with a bioavailability ranging from 76 to 88% [102].

Furthermore, in animal models, the distribution of CZP into inflamed tissue compared with normal tissue seems to be greater and more prolonged than that observed with adalimumab and infliximab; it is probable that these features are conferred to the drug by PEGylation [27]. After subcutaneous administration the estimated clearance rate was 21 ml/h [102].

Only bodyweight and the presence of antibodies to CZP affect the pharmacokinetics; the exposure to CZP is inversely related to bodyweight, but pharmacodynamic exposure-response analyses have demonstrated no additional therapeutic benefit in a weight-adjusted dose regimen; the presence of antibodies to CZP was associated with a 3.6-fold increase in clearance [102]. No pharmacokinetic differences were observed in relationship to age, sex and race [18].

The major elimination route is renal [36,102].

**Clinical efficacy**

Certolizumab pegol is approved in the USA, Canada and Europe for the treatment of patients with moderately-to-severely active RA; after a loading dose of 400 mg at weeks 0, 2 and 4 it is administered at the dose of 200 mg every 2 weeks or (in the USA) 400 mg at 4-week intervals by subcutaneous injection.

The efficacy and safety of CZP in combination with MTX or in monotherapy has been investigated in a Phase II, and afterwards, in three Phase III clinical trials [32–35].

- **Phase I studies**
In 1999, a Phase I study showed that therapeutic doses of CZP (CDP870) were well tolerated and produced no serious side effects in healthy volunteers. Both subcutaneous and intravenous formulations produced comparable results [103].

- **Phase II trials**
In a Phase II double-blind study, 36 patients with active RA, who had previously received an average of five DMARDs were randomized to receive CZP at 1, 5 or 20 mg/kg as a single infusion or placebo [32].

  The major outcomes were ACR20 (defined as a 20% improvement in the ACR Symptomatic Criteria) and safety [37,38].

  At weeks 4 (Table 2) and 8 (Table 3) the ACR20 response rate was respectively 66.7 and 58.3% in the combined CZP group versus 16.7% in the placebo group.

- **Phase III trials**

  **Certolizumab pegol plus MTX.**
  Two Phase III, multicenter, randomized, placebo-controlled trials evaluated the clinical efficacy in improving symptoms and preventing radiographic progression and safety of CZP plus MTX in adult patients with active RA despite treatment with MTX: RA Prevention of Structural Damage (RAPID) 1 and RAPID 2 [33,34].

  **Design**
  The RAPID 1 and 2 trials were 52 and 24 week trials respectively, involving 982 and 619 patients on a stable dose of MTX (≥10-mg weekly) who were randomly assigned to CZP (400 mg at weeks 0, 2 and 4, followed by either 200 or 400 mg every 2 weeks) or placebo. Patients who

### Table 2. Phase II study in rheumatoid arthritis: ACR and DAS28 response rate at 4 weeks.

<table>
<thead>
<tr>
<th>End point</th>
<th>Placebo (%)</th>
<th>1 mg/kg (%)</th>
<th>5 mg/kg (%)</th>
<th>20 mg/kg (%)</th>
<th>Combined p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>16.7</td>
<td>50.00</td>
<td>87.5</td>
<td>62</td>
<td>0.012</td>
</tr>
<tr>
<td>ACR50</td>
<td>0.00</td>
<td>12.5</td>
<td>12.5</td>
<td>50.00</td>
<td>0.079</td>
</tr>
<tr>
<td>DAS28</td>
<td>0.15</td>
<td>1.14</td>
<td>1.91</td>
<td>1.95</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data taken from [32].
did not achieve an ACR20 response at weeks 12 and 14 were withdrawn from the study at week 16 and allowed to enter an open-label extension study of CZP.

Two formulations of CZP were investigated; a lyophilized formulation in RAPID 1 and a liquid formulation in RAPID 2. Primary outcomes were ACR20 at week 24 (RAPID 1 and 2) and change from baseline in modified total Sharp score (mTSS) at week 52 (RAPID 1). Important secondary outcomes included ACR50 and ACR70 at week 24 (RAPID 1 and 2), Health Assessment Questionnaire disability index (HAQ-DI) at weeks 24 (RAPID 1 and 2) and 52 (RAPID 1) and mean change from baseline in the mTSS at week 24 (RAPID 1 and 2).

**Major results**

In the RAPID 1 trial, ACR20 responder rates at week 24 were significantly higher in patients who received CZP (200 or 400 mg) plus MTX than placebo plus MTX (58.8 and 60.8 vs 13.6%; p < 0.001 for each comparison). These differences remained significant at week 52. Treatment with CZP was also associated with improvement in the Disease Activity Score 28 (DAS28)-ESR at week 52 with a statistically significant difference compared with placebo (p < 0.001).

In the RAPID 2, trial ACR20 responder rates at week 24 were significantly higher in patients who received CZP (200 or 400 mg) plus MTX than placebo plus MTX (57.3 and 57.6 vs 8.7%; p < 0.01). Differences in ACR50 and ACR70 response were higher than placebo at week 24 both in RAPID 1 and RAPID 2 trials (Figures 2-4). Efficacy was evident at week 1, by which time CZP-treated patients were more likely to have achieved an ACR20 response (23 and 22 vs 6%). At week 24, patients treated with CZP were more likely to achieve an ACR50 (37 and 40 vs 8% in RAPID 1; 33 and 33 vs 3% in RAPID 2) or ACR70 (21 and 21 vs 3% in RAPID 1; 16 and 10 vs 0.8% in RAPID 2). The efficacy of CZP in inhibiting radiographic progression investigated in RAPID 1 and 2. In RAPID 1 at week 52, mean radiographic progression from baseline (mean change in mTSS) was significantly lower in the patients treated with CZP 200 mg (+0.4) and 400 mg (+0.2) versus placebo-treated patients (+2.8) (p < 0.001); a significant difference was also observed at week 24. No difference between the 200- and 400-mg CZP groups was observed on the inhibition of the progression of erosion and joint space narrowing.

In RAPID 2, mean changes in mTSS were significantly less in patients treated with CZP 200 mg (0.2) and 400 mg (-0.4) plus MTX versus placebo plus MTX (1.2) after 24 weeks in the RAPID 2 trial. Inhibition of the progression was observed in both trials as early as 16 weeks of treatment. Improvement in physical function was assessed using the HAQ-DI; in the RAPID 1 trial improvement was evident in both groups of CZP-treated patients (200 and 400 mg, respectively) at week 1 (HAQ-DI mean change -13.5 and 10.9 vs -2.4 of the placebo group). This improvement was sustained through week 52 (-0.60 and -0.63 vs -0.18).
In RAPID 2 from week 1 to 24 more, treated patients reported a significant improvement in physical function compared to the placebo groups. At week 24 in the CZP 200- and 400-mg group, 57 and 53% of patients achieved a meaningful improvement of HAQ-DI versus 11% of placebo patients (p< 0.001).

**Certolizumab pegol as monotherapy**
The efficacy and safety of CZP as monotherapy was also evaluated in adult patients with active RA who have failed at least one prior DMARD therapy in a 24-week placebo-controlled, double-blind trial, the FAST4WARD study [35].

**Design**
Randomized 24-week trial of 220 patients allocated to receive subcutaneous injections of either CZP (400 mg every 4 weeks; n = 111) or placebo (n = 109). The primary outcome was the ACR20 response at week 24. Important secondary outcomes were ACR50 and ACR70 at week 24, HAQ-DI, patient reported pain, health-related quality of life and safety.

**Major results**
The proportion of patients achieving an ACR20 response was significantly greater with CZP at week 24 (45.5 vs 9.3% with placebo; p < 0.001). Significant differences for ACR20 responses between CZP and placebo were evident after 1 week of therapy. CZP-treated patients were more likely to achieve ACR50 and ACR70 responses at week 24 (22.7 vs 3.7; p < 0.001; and 5.5 vs 0%; p < 0.05; respectively) (Figure 4). Improvements were observed in all components of the ACR core measures set. Physical function was significantly improved by week 1 (HAQ-DI of -0.23 vs +0.04) and through week 24 (-0.36 vs +0.13). A significant decrease in arthritis pain from baseline (by visual analog scale) was also noted at week 1 (-16.7 vs -5.2) and through week 24 (-20.6 vs +1.7). Significant improvements were also observed in disease activity heath-related quality of life and fatigue. Radiographic assessment was not performed.

**Postmarketing surveillance**
There have been no reports of new safety signals in postmarketing surveillance.

**Safety & tolerability**
In 2009 a safety update was published [39]. Adverse event data were pooled from all of the randomized and open-label trials of CZP. Up to August 2007, 2367 treated patients were analyzed.

Most adverse events were mild-to-moderate. The most frequent adverse event leading to discontinuation were infections: 61.2% (65,8/100 patient years); the most common serious infections were respiratory tract infections and tuberculosis. The most frequent noninfectious adverse events observed were headache, back pain and hypertension. The malignancy standardized
ratio rate was 1.22 (95% CI: 0.82–1.74); the lymphoma standardized ratio was 4.10 (95% CI: 0.84–11.97). The standardized mortality ratio was 0.96 (95% CI: 0.65–1.36) (Table 4).

More recently, a Cochrane overview on adverse effects of biologic therapies was published [40]. The authors included in the analysis 163 randomized clinical trials with 50,010 participants and 46 extension studies with 11,954 participants. Adjusted for dose, biologics as a group were associated with a statistically significant higher rate of total adverse events (odds ratio [OR]: 1.19; 95% CI: 1.09–1.30; number needed to treat to harm [NNTH]: 30; 95% CI: 21–60) and withdrawals due to adverse events (OR: 1.32; 95% CI: 1.06–1.64; NNTH: 37; 95% CI: 19–190) and an increased risk of TB reactivation (OR: 4.68; 95% CI: 1.18–18.60; NNTH: 681; 95% CI: 143–14,706) compared with control. The rate of serious adverse events, serious infections, lymphoma and congestive heart failure was not statistically significantly different between biologics and control treatment. CZP was associated with a significantly higher risk of serious infections compared with control treatment (OR: 3.51; 95% CI: 1.59–7.79; NNTH: 17; 95% CI: 7–68). Although the overall numbers are relatively small, CZP was associated with significantly higher odds of serious infections compared with etanercept, adalimumab, abatacept, anakinra, golimumab, infliximab and rituximab.

**Regulatory affairs**

Certolizumab pegol is approved in the USA, Canada and Europe for the treatment of patients with moderate-to-severe active RA; as monotherapy and in combination with MTX in the USA and Canada and in combination with MTX in Europe; it is administered every 2 weeks by subcutaneous injection, and dosing at 4-week intervals means that it can be considered for maintenance therapy. In the USA, as maintenance therapy, certolizumab pegol may be given as 200 mg subcutaneously every 2 weeks or 400 mg every 4 weeks, while in Canada and Europe it is approved as 200 mg every 2 weeks only [41].

**Conclusion**

Certolizumab pegol is an effective treatment for RA. It is demonstrated that it improves the signs and symptoms of disease, quality of life and slows the progressive destruction of joints.

The clinical, radiographic and functional improvements were observed early in the course of treatment.

There are five anti-TNF-α agents approved for the treatment of patients with RA. Etanercept, adalimumab and infliximab have demonstrated clinical efficacy in patients with RA MTX-naive, MTX incomplete responders and those who have failed DMARD therapy [42–54].

Recently, another subcutaneous anti-TNF-α was approved for RA treatment, golimumab; it showed clinical efficacy in MTX-naive patients (with early disease), MTX incomplete responders and in anti-TNF-α failure patients [55–57]. Finally CZP demonstrated effectiveness in MTX incomplete responders and those who have failed DMARD therapy [53–55], but data on CZP efficacy and safety in patients who discontinued other anti-TNF-α agents due

![Figure 5. ACR response rate (%) at study end (week 24) in the FAST4WARD trial.](image)

ACR: American College of Rheumatology; CZP: Certolizumab pegol.

<table>
<thead>
<tr>
<th><strong>Table 4. Pooled safety from randomized trials and open label extension studies.</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
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<tr>
<td>Any AE</td>
</tr>
<tr>
<td>SAE</td>
</tr>
<tr>
<td>AE leading to death</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
</tr>
<tr>
<td>Serious infections</td>
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<tr>
<td>Lower respiratory tract and lung</td>
</tr>
<tr>
<td>TB</td>
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<tr>
<td>Cardiac disorders</td>
</tr>
<tr>
<td>Ischemic coronary heart disorders</td>
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<tr>
<td>Rate and rhythm disorders</td>
</tr>
</tbody>
</table>

All certolizumab pegol doses: n = 2367. Exposure (patient years): 4065.2
AE: Adverse event; SAE: Serious adverse event.
Data taken from [39].
to adverse effects or ineffectiveness are still lacking. The question is which anti-TNF-α to use first.

Indirect meta-analyses of biologic DMARDs, using a hierarchical linear mixed model, concluded that there is no evidence that any of these drugs is superior or inferior to any other [20], but an important issue is the lack of head-to-head trials of CZP with any other DMARDs or other anti-TNF-α therapy.

The decision about prescribing one anti-TNF-α rather than another between all the available anti-TNF-α therapies is based on frequency and route of administration, patient preference and on the medical personal experience with that class of drugs. Patients have to be made aware that all anti-TNF-α agents exist and that all five are equally efficacious and safe.

Sometimes patients prefer self-administration whereas other patients prefer the intravenous route. Some patients prefer to take medication less frequently and others prefer to take drugs weekly in order to remember it easier.

Certolizumab pegol offers the advantage of a relatively rapid onset of action, infrequent administration, potential sparing of Fc dependent cytotoxicity and a potentially preferable anti-TNF-α antagonist choice for women of childbearing age because of its inability to cross the placenta.

A recent Cochrane meta-analysis on adverse events associated with biological therapies showed a higher risk for serious infections for CZP compared with the other biological DMARDs but there was no consistency across the outcomes so caution is needed in interpreting these results [40].

More data on the long-term safety of biologics and the comparative safety of different biologics is required; the development of national and international registries could be of great support to increase our knowledge regarding this point.

**Future perspective**

For a better and more informed choice of the right therapy for patients with RA there is a need for head-to-head randomized clinical trials comparing the effectiveness of DMARDs.

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**Executive summary**

**Pharmacokinetic properties**
- Apparent volume of distribution 6–8 l (steady state).
- Total body clearance 21 ml/h.
- Terminal elimination half-life: 14 days.
- Route of elimination: renal.

**Clinical efficacy**
- Three Phase III randomized clinical trials:
  - RAPID 1 and 2 demonstrated clinical efficacy in improving symptoms and preventing radiographic progression of certolizumab pegol plus methotrexate in adult patients with active rheumatoid arthritis despite treatment with methotrexate.
  - FAST4WARD trial showed certolizumab pegol efficacy versus placebo when used in monotherapy in patients with active rheumatoid arthritis who have failed at least one prior disease modifying antirheumatic drug therapy.

**Safety & tolerability**
- Most adverse events were mild-to-moderate.
- The most frequent adverse event leading to discontinuation were infections.
- The most common serious infections were respiratory tract infections and tuberculosis.
- The most frequent non-infectious adverse events observed were headache, back pain and hypertension.

**Dosage & administration**
- Dosage: 200 mg every 2 weeks or 400 mg every 4 weeks.
- Route: subcutaneous.
- Frequency: 400 mg at weeks 0.2 and 4 followed by 200 mg every 2 weeks (USA and EU); 400 mg every 4 weeks can be considered for maintenance dosing in the USA.

**Scheduled indication**
- Treatment of moderate-to-severe rheumatoid active arthritis in combination with methotrexate in adults who failed therapy with conventional disease modifying antirheumatic drugs including methotrexate.
- As monotherapy in case of intolerance to methotrexate or when continuing treatment is inappropriate.

**Contraindications**
- Hypersensitivity to the active substance.
- Active, severe infections (including tuberculosis, sepsis and opportunistic infections).
- Severe heart failure.

**Cost**
- £715 for two syringes each containing 200 mg of certolizumab pegol.
- £10,367.50/first year (including loading dose).
- £9295/year (considering 1 fl 200 mg subcutaneously every 2 weeks for a total of 26 doses/year).
Data is also needed on the efficacy of CZP in patients that have shown an intolerance or an incomplete response to a previous anti-TNF-α therapy.

Existing data reveal the importance of an early diagnosis and afterward of an early treatment of RA. Characterizing the variables that affect the disease’s evolution could make it possible to apply a more aggressive therapeutic approach in that subgroup of patients with a poor prognosis.

Certolizumab could have many other potential target diseases; it could be used in ankylosing spondylitis, in seronegative spondyloarthropathy, especially in psoriatic arthritis and in the inflammatory bowel disease-associated spondyloarthritis. In particular, in this last setting of patients, considering its demonstrated efficacy in Crohn’s disease, it could be, together with adalimumab and infliximab, one of the better treatments to target both diseases (the intestinal and articular one) at the same time.

Finally, we think that it is important for the clinicians to have another efficacious and safe drug available as a part of the armamentarium for RA treatment and future studies could be addressed to find the subgroup of patients in which this treatment is more effective.

In future, the development of oral small molecules, which are as effective as the currently available therapies, could most likely change the management of RA patients [58].

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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** The most complete overview of the randomized clinical trials on biological therapy for RA with indirect comparison of all therapies available.

** Drug Evaluation **

**Certolizumab pegol for the treatment of rheumatoid arthritis**

- A review of the DMARDs (synthetic and biologic) therapy for RA.


- Interesting comparison between anti TNF-α in RA.


- Indirect comparison between all the anti-TNF-α available for RA therapy.


- Interesting comparison between combined therapy with anti-TNF-α and MTX and monotherapy with MTX.


- The first Phase III randomized clinical trials on certolizumab plus DMARDs for the treatment of RA.


- The second Phase III trial on certolizumab plus DMARDs for the treatment of RA.


- The first Phase III trial on certolizumab monotherapy for the treatment of RA.

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- A possible new approach to treat RA with a small oral molecule.

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