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

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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

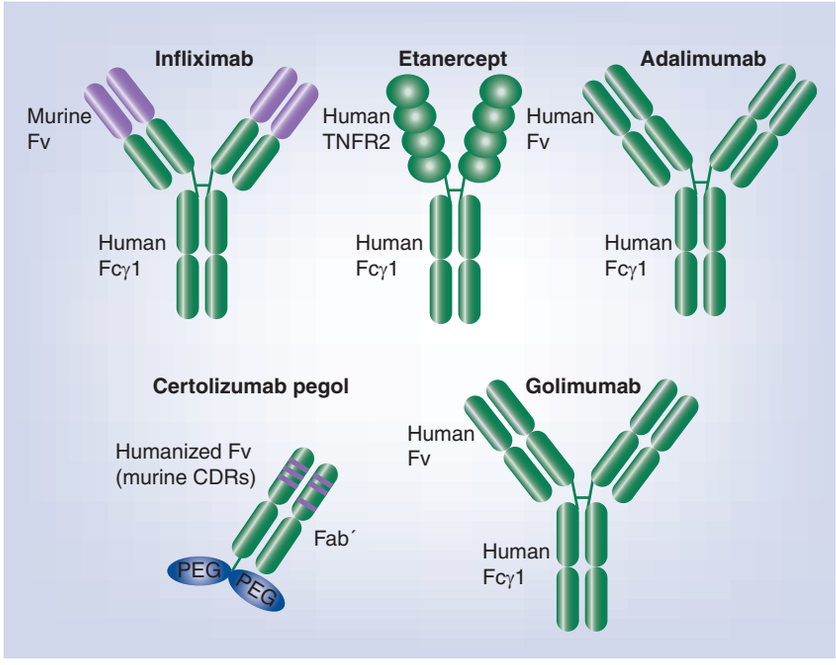

Figure 1. Molecular structures of TNF antagonists.
CDR: Complementarity-determining region; PEG: Polyethylene glycol; TNFR: Tumor necrosis factor receptor.

(TNFR:Fc). Etanercept is administered by subcutaneous injection once or twice weekly. It was approved in the USA for the treatment of RA in 1998.

Infliximab is a chimeric (human/murine) IgG1 monoclonal antibody directed against TNF. Infliximab is administered via intravenous infusion, at week 0, 2, 6 and every 8 weeks thereafter. It was approved in the USA for treatment of RA in 1998.

Adalimumab is a fully humanized IgG1 monoclonal antibody that inhibits TNF. Adalimumab is administered every 2 weeks by subcutaneous injection. It was approved in the USA for the treatment of RA in 2002.

Golimumab is a human IgG1-κ monoclonal antibody specific for human TNF-α that neutralizes TNF-α activity. It is usually administered once monthly by subcutaneous injection, but has also been studied using less frequent intravenous infusions. It was approved in the USA for the treatment of RA in 2010.

Currently, the existing data, derived from indirect comparison, showed no difference in terms of the efficacy and safety for all anti-TNF-α biologic treatments that are available for treating RA [19–25,102].

In fact, in 2010, an 'Overview of Cochrane Reviews' was published in The Cochrane Library [20], in which six biologic DMARDs were included (abatacept, adalimumab, etanercept, infliximab, anakinra and rituximab). Five 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 administred 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.

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

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

Author (year)	Trial	Groups	Number of patients	ACR50 6 month	ACR50 12 month	ACR50 24 month	Ref.
Lipsky *et al.* (2000)	IFX + MTX vs MTX	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	86 86 87 81 340 88 428	22/86 25/86 27/87 21/81 95/340 4/88	18/86 29/86 34/87 31/81 112/340 7/88	NA	[42]
St Clair *et al.* (2004)	IFX + MTX vs MTX	3 mg/kg 8 weeks + MTX 6 mg/kg 8 weeks + MTX Total IFX MTX Total	373 378 751 298 1049	NA	171/373 189/378 360/751 161/298	NA	[43]
Quinn *et al.* (2005)	IFX + MTX vs MTX	3 mg/kg 8 weeks + MTX MTX total	10 10 20	NA	08/10 4/10	NA	[44]
Westhovens *et al.* (2006)	IFX + MTX vs MTX	3 mg/kg 8 weeks + MTX 10 mg/kg 8 weeks + MTX Total IFX MTX Total	360 361 721 363 1084	110/360 119/361 229/721 33/363	NA	NA	[45]
Moreland *et al.* (1999)	ETN vs placebo	25 mg twice weekly 10 mg twice weekly Total ETN Placebo Total	78 76 154 80 234	31/78 18/76 49/154 4/80	NA	NA	[46]
Weinblatt *et al.* (1999)	ETN + MTX vs MTX	25 mg + MTX MTX Total	59 30 89	23/59 1/30	NA	NA	[47]
Bathon *et al.* (2000)	ETN vs MTX	25 mg twice weekly 10 mg twice weekly Total ETN MTX Total	207 208 415 217 632	NA	101/207 NA NA 93/217	NA	[48]
Van der Heijde *et al.* (2006)	ETN + MTX vs ETN vs MTX	25 mg twice weekly + MTX 25 mg twice weekly Total ETN MTX Total	231 223 454 228 682	NA	159/231 107/223 266/454 98/228	164/231 120/223 284/454 96/228	[49]
Weinblatt *et al.* (2003)	ARMADA ADA + MTX vs MTX	40 mg/2 weeks + MTX 20 mg/2 weeks + MTX 80 mg/2 weeks + MTX Total ADA MTX Total	67 69 73 209 62 271	37/67 22/69 31/73 90/209 5/62	NA	NA	[50]
van de Putte *et al.* (2004)	ADA vs placebo	40 mg/2 weeks 20 mg/2 weeks 20 mg/week 40 mg/week Total ADA Placebo Total	113 106 112 103 434 110 554	25/113 20/106 23/112 36/103 104/434 9/110	NA	NA	[51]
Furst *et al.* (2003)	STAR ADA + DMARDs vs DMARDs	40 mg/2 weeks DMARD Total	318 318 636	93/318 35/318	NA	NA	[52]

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.

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

Author (year)	Trial	Groups	Number of patients	ACR50 6 month	ACR50 12 month	ACR50 24 month	Ref.
Keystone *et al.* (2004)	ADA + MTX vs MTX	40 mg/2 weeks + MTX 20 mg/week + MTX Total ADA MTX Total	207 212 419 200 619	80/207 87/212 167/419 19/200	86/207 80/212 166/419 19/200	NA	[53]
Breedveld *et al.* (2006)	PREMIER ADA + MTX vs ADA vs MTX	40 mg/2 weeks + MTX 40 mg/2 weekS Total ADA MTX Total	268 274 542 257 799	NA	166/268 112/274 278/542 118/257	158/268 101/274 259/542 111/257	[54]
Keystone *et al.* (2008)	RAPID 1 CZP + MTX vs MTX	CZP 200 mg/2 weeks + MTX CZP 400 mg/2 weeks + MTX Total CZP MTX + placebo Total	393 390 783 199 982	145/393 (37.1%) 155/393 (39.9%) 300/783 15/199 (7.6%)	NA	NA	[33]
Smolen *et al.* (2009)	RAPID 2 CZP + MTX vs MTX	CZP 200 mg/2 weeks + MTX CZP 400 mg/2 weeks + MTX Total CZP MTX + placebo Total	246 246 492 127 619	80/246 (32.5%) 81/246 (33.1%) 161/492 4/127 (3.1%)	NA	NA	[34]
Fleischmann *et al.* (2009)	FAST4WARD CZP vs MTX	CZP 400 mg/4 weeks Placebo	111 109 220	25/111 (22.7%) 4/109 (3.7%)	NA	NA	[35]
Fleischmann *et al.* (2008)	GO-BEFORE GLM + MTX vs GLM vs MTX	GLM 100 mg/4 weeks GLM 100 mg/4 weeks + MTX GLM 50 mg/4 weeks + MTX Total GLM MTX Total	159 159 159 477 160 637	52/159 (32.7%) 58/159 (36.5) 64/159 (40.3 47/160 (29,4%)	NA	NA	[55]
Keystone *et al.* (2009)	GO-FORWARD GLM + MTX vs GLM vs MTX	GLM 100 mg/4 weeks GLM 100 mg/4 weeks + MTX GLM 50 mg/4 weeks + MTX Total GLM MTX + placebo Total	133 133 89 355 89 444	26/133 (19.5%) 43/133 (32.6%) 33/89 (37.1%) 102/355 12/89 (13.5%)	NA	NA	[56]
GO AFTER (2009)	GLM vs Placebo	GLM 50 mg/4 weeks GLM 100 mg/4 weeks Total GLM Placebo Total	153 153 306 155 461	28/153 (18.3%) 31/153 (20.3%) 59/306 8/155 (5.2%)	NA	NA	[57]

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.

dosing every 2 or 4 weeks (minimum 2 weeks). In addition, PEGylation 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].

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 C_{max}. In multiple dose studies, following the loading dosage there was a C_{max} of 39–43 µg/ml at week 5 [102]. The C_{max} 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.

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

Data taken from [32].

Table 3. Phase II study in RA: ACR and DAS28 response rate at 8 weeks.

End point	Placebo (%)	1 mg/kg (%)	5 mg/kg (%)	20 mg/kg (%)	Combined p-value
ACR20	16.7	25.00	75.00	75.00	0.032
ACR50	0.00	12.5	12.5	50.00	0.079
DAS28	0.03	0.09	2.09	1.76	0.008

ACR: American College of Rheumatology; DAS: Disease Activity Score; RA: Rheumatoid arthritis.
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 ($p < 0.001$).

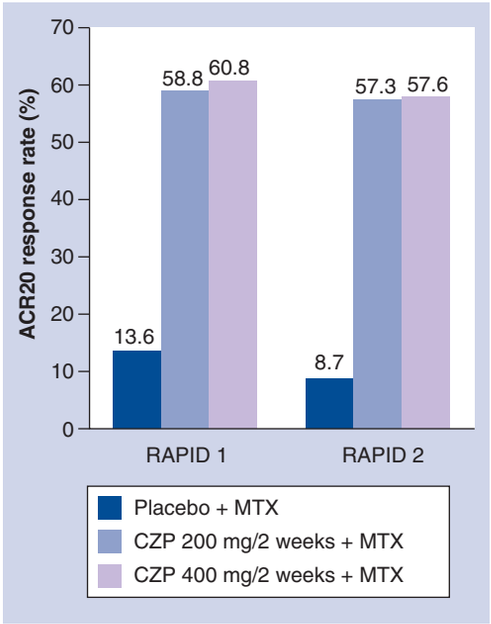

Figure 2. ACR20 response rate (%) at week 24 in RAPID1 and RAPID2 trials.
ACR: American College of Rheumatology; CZP: Certolizumab pegol; MTX: Methotrexate.

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 of -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 5). 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.

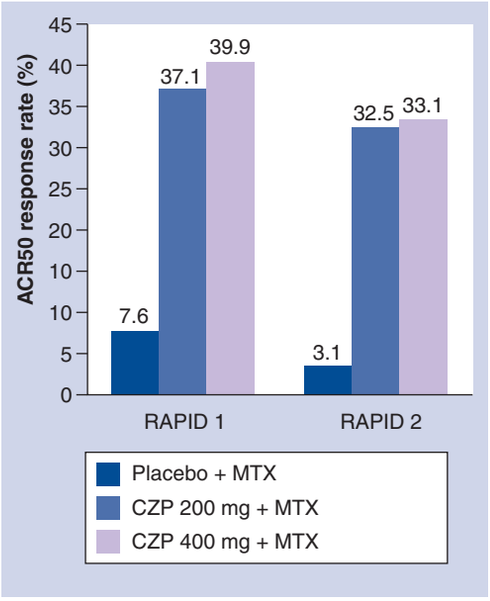

Figure 3. ACR50 response rate (%) at week 24 in RAPID1 and RAPID2 trials.
ACR: American College of Rheumatology; CZP: Certolizumab pegol; MTX: Methotrexate.

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

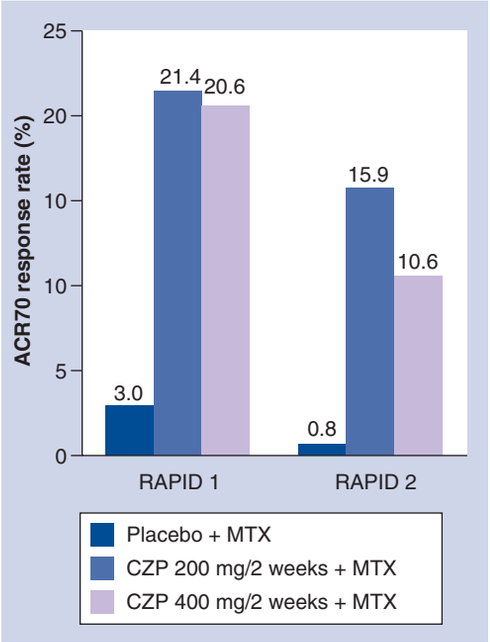

Figure 4. ACR70 response rate (%) at week 24 in RAPID1 and RAPID2 trials.
ACR: American College of Rheumatology; CZP: Certolizumab pegol; MTX: Methotrexate.

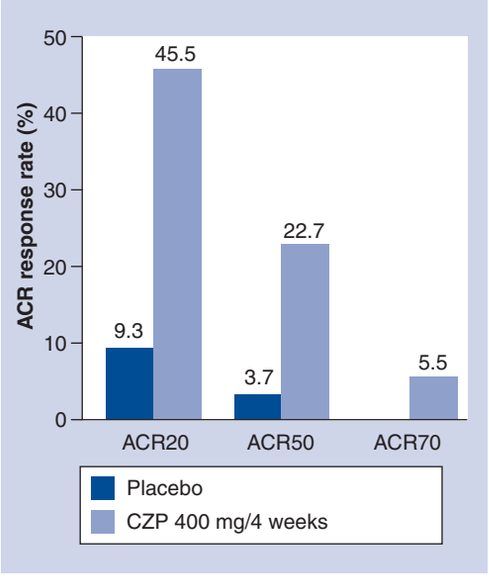

Figure 5. ACR response rate (%) at study end (week 24) in the FAST4WARD trial.
ACR: American College of Rheumatology; CZP: Certolizumab pegol;

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.

Table 4. Pooled safety from randomized trials and open label extension studies.

Adverse events	Incidence/100 patient years	%
Any AE	183.1	86.1
SAE	17	26
AE leading to death	1.27	1.4
AEs leading to withdrawal	6.5	12.2
Serious infections	5.3	8.9
Lower respiratory tract and lung	1.3	2.2
TB	0.7	1.3
Cardiac disorders	4.3	7.3
Ischemic coronary heart disorders	1.1	1.9
Rate and rhythm disorders	1.1	1.9

All certolizumab pegol doses: n = 2367.
Exposure (patient years): 4065.2
AE: Adverse event; SAE: Serious adverse event.
Data taken from [39].

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 maintanence 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 [33–35], but data on CZP efficacy and safety in patients who discontinued other anti-TNF-α agents due

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.

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 maintanence 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 spondyloarthopathy. 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.

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