Published in final edited form as:

Expert Rev Clin Immunol. 2010 November ; 6(6): 855–866. doi:10.1586/eci.10.69.

Certolizumab pegol: a new biologic targeting rheumatoid arthritis

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Abstract

The past decade has been an exciting period for clinical research and patient care in rheumatoid arthritis. This is mostly due to targeted biologic agents that have changed the outcome of this disease. Certolizumab pegol (Cimzia®, UCB Inc., GA, USA), which targets TNF- α with a different mechanism of action than widely used biologics, was initially investigated for Crohn's disease but has now been shown to be effective for rheumatoid arthritis. There have been three significant clinical trials demonstrating the efficacy of certolizumab pegol in active rheumatoid arthritis; two with combination methotrexate and one with monotherapy. This article will summarize the data from those trials and compare some of the characteristics of certolizumab pegol to conventional disease-modifying antirheumatic drugs and other biologic agents. Treatment recommendations are beyond the scope of this review; however, with many options available, there will be annotations on current trends in the care of this chronic disease.

Keywords

anti-TNF- α therapy; biologics; certolizumab pegol; rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic disease that has complex genetic and environmental factors acting together to cause inflammation and damage. This occurs primarily in the synovium and joint tissues; however, there is also other organ involvement. The typical clinical features are swollen, painful joints and stiffness. Important extra-articular features include lung disease and cardiovascular disease. Other manifestations can include anemia, fatigue, skin nodules, neuropathy, ocular disease, splenomegaly, vasculitis and pleuropericarditis [1,2].

In many populations, there is a range of 0.5–1% prevalence, with a higher occurrence in Chippewa and Pima Indians and a lower occurrence in the Chinese and Japanese, supporting a genetic role in pathogenesis [2]. Women are affected up to three-times as much as men [3].

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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.

The annual incidence of RA has been shown to be approximately 30 per 100,000 population [3]. This disease can occur at any age, with peak onset between 30 and 55 years of age [3].

Joint damage can take place at disease onset, therefore, early aggressive therapy with the goal of remission is preferred by most clinicians to prevent disability, economic loss and mortality [4,5]. The course of disease is variable, with approximately 15–20% of patients having intermittent disease with a good prognosis [1]. Despite the wide use of disease-modifying antirheumatic drugs (DMARDs) and biologic agents in various combinations, some patients still have persistently active disease. Current recommendations by the American College of Rheumatology (ACR) deal with the indications for DMARDs and biologic agents. These guidelines account for screening for TB, sideeffect monitoring, clinical response assessment, patient preference and cost. However, each patient is treated individually based on disease activity, prognostic signs and functional impairment. There is a strong recommendation to use a biologic agent only after failure of nonbiologic DMARDs unless high disease activity is present with poor prognostic signs [5,6].

Overview of the market

Small-molecule or nonbiologic DMARDs include methotrexate (MTX), leflunomide, sulfasalazine and hydroxychloroquine; they are all used as first-line agents (some in combination) in RA, with MTX being the dominant medication. Azathioprine, cyclosporine and gold agents are older and are used rarely these days. There is also a role for low-dose, long-term corticosteroids in some patients [7,8]. Those with persistently active disease after a trial of one DMARD are usually placed on either combination DMARDs [9] or biologic agents. There are guidelines by NICE that advocate combination DMARDs (MTX and at least one other DMARD) as first-line therapy [101]. Biologic agents in combination with a DMARD such as MTX are at times used as first-line therapy; however, MTX as monotherapy and combination small-molecule DMARDs have good efficacy in some patients [10–12]. This topic remains controversial as the cost-effectiveness of biologics as first-line therapy is not as high when compared with traditional DMARDs as first-line therapy [13].

TABLE 1 lists the biologic agents approved in the USA [102] and Europe [103] for RA. Etanercept is a recombinant soluble p75 receptor for TNF- α . Infliximab and adalimumab are anti-human TNF- α monoclonal antibodies. Many trials have shown the effectiveness of these three biologics that are traditionally administered prior to the others [10–12,14–19].

Second- and third-line agents are commonly used after a patient has failed one or more biologic [20–23]. These newer agents are available and widely used for persistently active disease; however, there are no strict guidelines in choosing a drug or class. Golimumab, a TNF inhibitor that can be administered monthly, has shown efficacy when other TNF agents have failed [24]. It should be noted that there are data from observational studies showing that other TNF inhibitors are effective in patients who have failed one TNF inhibitor [23]. Abatacept is a cytotoxic T-lymphocyte-associated antigen-4-immunoglobulin fusion protein that has been used with success in patients refractory to DMARDs and other biologics [21,25,26]. Rituximab, a monoclonal antibody to CD20, depletes B lymphocytes and is used in many autoimmune disorders as well as RA refractory to other treatments [20]. IL-6 inhibition with tocilizumab, a humanized anti-IL-6 receptor antibody, has shown significant efficacy in RA patients [22,27] and was recently approved in the USA and Europe. Anakinra is an IL-1 antagonist that is effective in RA and is administered as a daily injection, making it less convenient for some and therefore it is used rarely [28].

Patients do not respond to DMARDs and biologics equally and encounter problems with adverse effects and tolerance. In lieu of this, many new agents are being developed, with

some in trials at the time of this publication. Inhibitors of osteoclastogenesis (denosumab) and an inhibitor of B lymphocytes (ocrelizumab) have recently shown efficacy in RA [29,30]. Newer therapies are targeting IL-1 (canakinumab), cytokines from the TNF superfamily (atacept), IL-15 (HuMaxIL-15), IL-17 (AIN457), B lymphocytes (ofatumumab and TRU-015), IL-12/IL-23 (apilimod and STA-5326), SyK kinase (fostamatinib) and JAK3 kinase (CP-690,550) [30–40]. This list is not complete as many more therapies are in the developmental stages.

Chemistry

Certolizumab pegol (CZP) is a PEGylated Fab' fragment of a humanized monoclonal antibody that is prepared in *Escherichia coli* with the end product being specific for human TNF- α with a disassociation constant (KD) of approximately 90 pM. The fragment is made of a light chain (214 amino acid residues) and a heavy chain (229 amino acid residues). The weight of CZP is approximately 90.8 kDa. CZP will neutralize membrane-associated and soluble human TNF- α in a dose-dependent manner but it does not neutralize TNF- β . There is also a dose-dependent inhibition of lipopolysaccharide-induced TNF- α and IL-1 β when CZP is incubated with human monocytes [104].

When comparing this drug with other TNF inhibitors, CZP has a difference in its mechanism. *In vitro*, this drug will not induce apoptosis in human peripheral blood-derived monocytes or lymphocytes [41]. CZP does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro* because of the lack of a fragment crystallizable region, which is usually present in a complete antibody. There is also no induction of neutrophil degranulation *in vitro* that is seen in the other TNF inhibitors [104]. There was no cross-reactivity of CZP seen with cryosections of normal human tissues in an *ex vivo* study [104,41].

Pharmacodynamics

Elevated levels of TNF- α are implicated in the pathogenesis of RA and found in the synovial fluid of patients. TNF- α has many biologic activities such as upregulation of cellular adhesion molecules and chemokines, upregulation of MHC class I and class II molecules, and direct leukocyte activation. The production of downstream inflammatory mediators such as IL-1, prostaglandins, platelet-activating factor and nitric oxide are all stimulated by TNF- α . The role that TNF- α plays in inflammation is inhibited by CZP [104].

Pharmacokinetics & metabolism

There are four pharmacokinetic studies of healthy individuals ($n = 126$) who received CZP (up to 800 mg subcutaneously and 10 mg/kg intravenously). These studies demonstrate that a single dose (subcutaneous and intravenous) has a predictable doserelated plasma concentration, with a linear relationship between administered doses and the maximum plasma concentration ($C_{\max}$). With the recommended dose for RA (CZP 400 mg subcutaneous at weeks 0, 2 and 4 followed by 200 mg every other week), a mean $C_{\max}$ of approximately 43–49 $\mu\text{g/ml}$ occurred at the fifth week. Plasma concentrations were broadly proportional to the dose administered and pharmacokinetics observed in the RA patients were similar to those seen in healthy individuals [104].

For all the doses tested, the terminal elimination half-life was approximately 14 days. In healthy subjects, the clearance (intravenous administration) ranged from 9.21 to 14.38 ml/h. In RA patients, the clearance (subcutaneous administration) was 21.0 ml/h. Bioavailability of approximately 80% (range 76–88%) was seen after subcutaneous administration compared with intravenous administration. The $C_{\max}$ was reached between 54 and 171 h

after subcutaneous administration. Metabolism has not been studied in humans; however, animal data show that once the PEG moiety is cleaved from the Fab' fragment, it is excreted in urine [104].

Pharmacokinetic exposure was inversely related to bodyweight of subjects; however, pharmacodynamic studies show that there is no therapeutic benefit of adjusting the dose according to bodyweight. Anti-CZP antibodies significantly affected the pharmacokinetics of CZP (3.6-fold increase in clearance). Age, gender and race (Caucasian and Japanese) had no bearing on the pharmacokinetics of CZP. The pharmacokinetics of CZP when there is renal impairment will need to be studied. There are no data on the effect of MTX on CZP pharmacokinetics as well as drug–drug interactions with corticosteroids and NSAIDs. The pharmacokinetics of MTX are not altered by concomitant administration of CZP in RA. There are no data on the effectiveness or safety in pediatric patients and limited data on its use in geriatric patients [104].

Clinical efficacy

The efficacy of CZP in RA has been evaluated in three key trials, which are reviewed in the next section and summarized in Table 2. These studies evaluated active RA patient response to CZP monotherapy and combination therapy (two separate doses) with MTX compared with placebo. The duration ranges from 24 to 52 weeks, with clinical outcomes and patient-reported outcomes (PROs) being assessed [42–44]. The RAPID 1 trial has long-term extension data available that are also reviewed in the next section [45–47]. Work productivity was assessed using both the RAPID 1 and RAPID 2 cohorts, and is summarized [48].

Certolizumab pegol plus MTX in active RA (RAPID 1)

Study aims & methods

The aim of RAPID 1 was to compare two dosage regimens of lyophilized CZP plus MTX versus placebo plus MTX in those with active RA who had an inadequate response to MTX alone. This was a 52-week, Phase III, multicenter randomized double-blind placebo-controlled parallel-group study. ACR defined RA patients with active disease who had received MTX for at least 6 months (stable dose of 10 mg/week for 2 months prior to baseline) were eligible for the study [49]. The patients were at least 18 years of age and had RA for at least 6 months but less than 15 years. Those who qualified had to have active disease defined as at least nine tender joints and more than nine swollen joints with either erythrocyte sedimentation rate (ESR) as at least 30 mm/h or C-reactive protein level above 15 mg/l. Those with other inflammatory conditions, high risk for infection, history of TB and any biologic therapy within 6 months of baseline were excluded. Patients were randomly assigned to three groups (2:2:1). Two groups received CZP at an initial dosage of 400 mg subcutaneously at weeks 0, 2 and 4, with the first group receiving a 200-mg dosage of CZP plus MTX every 2 weeks ($n = 393$); the second group received a subsequent 400-mg dosage of CZP plus MTX every 2 weeks ($n = 390$). The third group received placebo (saline every 2 weeks) plus MTX ($n = 199$). Treatment failures defined as ACR 20% improvement criteria (ACR20) nonresponders at week 12 and confirmed at week 14 were withdrawn (week 16) and had an option for an open-label extension phase (CZP 400 mg every 2 weeks). Statistical analysis was carried out in three different imputation methods. Logistic regression was applied on the ACR20 [50] response rate with missing data analyzed with nonresponder imputation. When applying analysis of covariance (ANCOVA) on the ranks on modified total Sharp score (mTSS) with baseline mTSS as covariate and treatment and region as factors, missing data were imputed by linear extrapolation of available data. The

last observation was carried forward in an ANCOVA with treatment and region as factors and baseline as covariates.

The coprimary end points were the ACR20 [50] response rate (week 24) and the mean change in mTSS (week 52) [51] from baseline. Major secondary end points were change from baseline in the following: mTSS (week 24), Health Assessment Questionnaire disability index (HAQ-DI) [52] (week 24 and 52), ACR20 response rate (week 52) and the ACR50/ACR70 response rates (weeks 24 and 52). There were additional secondary end points not already listed [42].

In the same study [47], PROs were assessed in depth as secondary end points. This included health-related quality of life (HRQoL) [53], which was measured using the Short-Form 36 Health Survey (SF-36) [54], and fatigue, which was measured by the Fatigue Assessment Scale (FAS) [55]. Physical function was measured using the HAQ-DI. Pain and patient's global assessment of disease activity were measured using a visual analog scale (VAS) [56]. These measures were assessed at multiple time points during the 52 weeks and analyzed on the intention-to-treat (ITT) population. The 2-year data on PROs, ACR response rate and radiographic progression from the RAPID 1 cohort were also analyzed and reported from the open-label phase of the study [45,46].

Study results

A total of 982 patients were randomized in RAPID 1. Of these, more patients in the two CZP groups completed 52 weeks of treatment (64.9% with 200 mg and 70.3% with 400 mg, $p < 0.001$ by logistic regression) compared with the placebo group (21.6%). Treatment failures (week 16) were higher in the placebo group (62.8%) compared with the two CZP groups (21.1% with 200 mg and 17.4% with 400 mg). The ACR20 response rates in the two CZP groups (58.8% with 200 mg and 60.8% with 400 mg) were higher than placebo (13.6%) at week 24 and remained significantly higher through week 52 ($p < 0.001$ by logistic regression). The ACR50/ACR70 response rates at week 24 in the two CZP groups (37.1/21.4% with 200 mg and 39.9/20.4% with 400 mg) were higher than placebo (7.6/3.0%). The mean change in mTSS from baseline was less in the CZP 200 mg group (0.4 Sharp units) and CZP 400 mg group (0.2 Sharp units) than in the placebo group (2.8 Sharp units) at week 52, and these changes were significant as early as week 24 ($p < 0.001$ by rank analysis).

The PROs demonstrated that HRQoL was significantly improved in the CZP groups compared with placebo from week 12 through week 52 ($p < 0.001$). Fatigue was also reduced significantly in the CZP groups compared with placebo from week 1 and was maintained throughout the study ($p < 0.001$). Patients in the CZP groups experienced clinically meaningful changes in their HAQ-DI from week 1 through week 52. The HAQ-DI reported by the CZP groups was reduced from 1.7 at baseline to 1.1 at week 52 and was significantly less than placebo ($p < 0.001$). From week 1 to week 52 there was a significant improvement in the pain VAS and patient's global assessment of disease activity in the CZP group compared with placebo ($p < 0.001$). The PROs response correlated with the clinical response (disease activity score using 28 joint counts [DAS28] and ACR20) in this cohort of patients [48].

The 2-year data on PROs (open-label phase) showed that improvements were sustained until at least week 100 [46]. The inhibition of radiographic damage was preserved for 2 years in the majority of patients in the CZP groups (72.4% in CZP 200 mg and 77.3% in CZP 400 mg). This was defined as an mTSS change of a maximum of 0.5 from baseline. The ACR20/ACR50/ACR70 responses were all maintained for 2 years in the open-label phase [45,46].

The results demonstrate that CZP plus MTX significantly reduced signs and symptoms of active RA and inhibited the progression of structural damage when compared with placebo in patients who had inadequate response to MTX and who continue to take MTX. PROs improved significantly in the two CZP groups when compared with placebo and were maintained for 2 years in the open-label phase.

Certolizumab monotherapy in active RA (FAST4WARD)

Study aims & methods

The aim was to evaluate the efficacy and safety of CZP as monotherapy in those with active RA who had inadequate response to one or more DMARDs. This was a 24-week, multicenter, randomized double-blind placebo-controlled study. ACR-defined RA patients aged 18–75 years who had disease for at least 6 months and had failed at least one DMARD from a lack of efficacy or tolerance were eligible for this study. Those who were eligible were screened to ensure that they had active disease (defined by at least nine tender joints and at least nine swollen joints). In addition, they had to have at least one of the following: at least 45 min of morning stiffness, ESR of 28 mm/h or greater, or C-reactive protein above 10 mg/l. Those with other inflammatory conditions, chronic or current infections, a history of TB, who had received biologic therapies within 6 months or who had ever received TNF- α inhibitors were excluded. Patients were randomly assigned (1:1) to receive 400 mg of subcutaneous CZP (n = 111) or placebo every 4 weeks (n = 109) from baseline to week 20. Those who completed the study or withdrew on/after week 12 were eligible to enter an open-label study of the drug (400 mg) every 4 weeks. Those who withdrew after taking at least one study dose were asked to return for an early withdrawal visit.

The primary end point of the study was the ACR20 response rate (week 24). The secondary end points included ACR50/ACR70 response rates, ACR component scores, DAS(ESR)3, PROs (HAQ-DI, HRQoL and SF-36), pain (measured by VAS and modified Brief Pain Inventory) and fatigue (measured by FAS) and safety. Analysis of results was performed on the modified ITT population. The proportion of ACR20 responders/non-responders at each visit was compared using the Cochran–Mantel–Haenszel (CMH) test stratified by country.

Study results

A total of 220 patients were randomized and received the drug. Significantly more patients in the CZP group (68.5%) completed 24 weeks of treatment compared with the placebo group (25.7%). Treatment failures were higher in the placebo group (68.8%) compared with the CZP group (21.6%). The ACR20 response rates in the CZP group (45.5%) were higher than placebo (9.3%) at week 24 using nonresponder imputation ($p < 0.001$ by CMH test). The ACR50/ACR70 response rates were also superior to placebo at week 24 ($p < 0.001$ and $p = 0.05$, respectively). All ACR components in the CZP group showed significant improvement at week 24 when compared with placebo ($p = 0.05$). The DAS28(ESR)3 change from baseline was superior in the CZP group (-1.5) versus placebo (-0.6) at all time points ($p < 0.001$). Patients in the CZP group experienced clinically meaningful changes in their HAQ-DI compared with placebo from week 1 (-0.23 vs 0.04, respectively) through to week 24 (-0.36 vs 0.13, respectively; $p < 0.001$). The HRQoL and SF-36 showed significant improvements in the CZP group compared with placebo at week 24 ($p < 0.001$). The CZP group experienced clinically meaningful reduction in pain (VAS and modified Brief Pain Inventory) by week 1 and improvements in fatigue (FAS) throughout the 24-week study compared with the placebo group.

This study is the first to demonstrate that CZP monotherapy administered subcutaneously every 4 weeks is efficacious in treating active RA patients who have failed one or more

DMARDs. This was shown clinically with ACR20 response and by multiple PROs throughout the study period (weeks 1–24).

Certolizumab pegol plus MTX in active RA (RAPID 2)

Study aims & methods

The aim of RAPID 2 was to evaluate the safety and efficacy of CZP plus MTX versus placebo plus MTX in those with active RA. This was a 24-week, Phase III, international, multicenter, randomized double-blind placebo-controlled study. ACR-defined RA patients with active disease who had received MTX for at least 6 months (stable dose 10 mg/week for 2 months prior to baseline) were eligible for the study. The patients were at least 18 years of age and had RA for at least 6 months but less than 15 years. Those with a history of TB or who had received etanercept or anakinra within 3 months or other biologics within 6 months of enrollment were not eligible. Patients were randomly assigned to three groups (2:2:1). Two groups received subcutaneous CZP at an initial dose of 400 mg at weeks 0, 2 and 4, with subsequent dosage of 200 mg CZP plus MTX (n = 246), or 400 mg CZP plus MTX every 2 weeks (n = 246). The third group received placebo (saline) plus MTX every 2 weeks (n = 127). The ACR20 nonresponders (weeks 12 and 14) were allowed to enter the open-label extension at week 16 (CZP 400 mg every 2 weeks). Efficacy analysis was performed on the ITT population and logistic regression with treatment and region as factors was used for primary analysis (nonresponder imputation for missing data after withdrawal or rescue medication intake). The primary end point was the ACR20 response rate (week 24). Secondary end points (all at week 24) included ACR50/ACR70 response rates, mean change in mTSS from baseline, SF-36 and individual ACR core set variables. The DAS28(ESR)4 was used to assess disease activity.

Study results

A total of 619 patients were randomized. Significantly more patients in the two CZP groups (70.7% with 200 mg and 73.6% with 400 mg) completed 24 weeks of treatment compared with the placebo group (13.4%). The ACR20 nonresponders (week 16) were higher in the placebo group (79.5%) compared with the two CZP groups (19.9% with 200 mg and 18.7% with 400 mg). The ACR20 response rates in the two CZP groups (57.3% with 200 mg and 57.6% with 400 mg) were higher than placebo (8.7%) at week 24 ($p < 0.001$ by logistic regression). The ACR50/ACR70 response rates at week 24 in the two CZP groups (32.5/15.9% with 200 mg and 33.1/10.6% with 400 mg) were higher than placebo (3.1/0.8%). The mean change in mTSS from baseline was less in the CZP 200-mg group (0.2 Sharp units) and CZP 400-mg group (−0.4 Sharp units) than in the placebo group (1.2 Sharp units) at week 24 ($p = 0.05$ by rank analysis). All ACR core components as well as the SF-36 in the CZP group showed significant improvement at week 24 ($p < 0.001$) when compared with placebo. The DAS28(ESR) mean change from baseline was superior in the CZP 200-mg group (−2.27) and CZP 400-mg group (−2.46) than in the placebo group (−0.50) at week 24 ($p < 0.001$).

This study showed that CZP plus MTX improved the clinical symptoms of disease, quality of life and increased physical function when compared with placebo plus MTX in those with active RA despite prior MTX therapy.

Effect of CZP on home & work productivity

Study summary

The aim was to evaluate the impact of CZP plus MTX on productivity inside and outside the home using the cohorts from RAPID 1 and RAPID 2. The RA-specific Work Productivity

Survey responses were obtained every 4 weeks throughout each study [57]. The study drug significantly reduced work absenteeism and presenteeism in those working outside their home compared with placebo. There were also significant reductions in the number of household days lost, household days with reduced productivity and days lost owing to RA for participation in other activities (leisure, social and family) in the CZP groups compared with placebo. There were improvements in all these measures from week 4 to the end of each study (24 weeks in RAPID 2 or 52 weeks in RAPID 1). These data showed that when the study drug was compared with placebo, there was improved productivity inside and outside the home consistent with clinical improvements.

Safety & tolerability

The most common adverse events (AEs) from CZP were upper respiratory infections, rash and urinary tract infections according to premarketing controlled trials. Pyrexia, urticaria, pneumonia and rash seen in 0.3% were the most common AEs that led to discontinuation in controlled clinical studies. Warnings and precautions when using CZP include: hepatitis B virus reactivation, hypersensitivity reactions, neurologic reactions, hematologic reactions, development of lupus-like syndrome and caution with use of other DMARDs. It is recommended that live vaccines are not to be administered [104].

The incidence of AEs and serious AEs (SAEs) from the study groups in the three key trials are summarized in TABLE 3. In these three trials, most patients tolerated CZP, with the majority of AEs being mild to moderate [42–44]. See TABLE 4 for a comparison of AEs reported by at least 3% of patients who took CZP every other week (n = 640) compared with those who took placebo + MTX (n = 324). In clinical trials, the AEs experienced by users taking CZP 200 mg every other week were similar to those taking CZP 400 mg every other week [104].

In RA clinical studies, the incidence of infections was 0.91 per patient-year for CZP-treated patients compared with 0.72 per patient-year for placebo-treated patients. These were mostly upper respiratory tract infections, herpes, urinary tract infections and lower respiratory tract infections. The incidence of serious infection for all CZP doses was 0.06 per patient-year compared with 0.02 per patient-year for placebo. Some examples of these infections that can be classified as SAEs include bacterial, invasive fungal, viral and other opportunistic infections. It should be noted that when an opportunistic infection occurs, it frequently presents as disseminated disease. It is advised not to use CZP when there is an active infection and to use caution in those at high risk of infection or recurrent infections [104].

Reactivation of TB, as well as new cases of TB, has been reported after receiving CZP; it is recommended that TB risk be evaluated prior to administration of this drug. In combined RA trial data, TB was the most common adverse reaction leading to discontinuation (0.5%) and there have been 36 cases of TB in those receiving CZP (n = 2367), with the majority occurring in countries endemic for TB [104]. A total of ten patients from the three trials reviewed developed TB; none were from North America [42–44].

Other SAEs that patients are at risk from when using CZP include malignancy and heart failure. In the controlled portions of clinical trials of TNF- α inhibitors, more cases of lymphoma have been seen in those who received TNF- α inhibitors compared with control patients. In combined RA trial data, the overall incidence of malignancy was similar in CZP and placebo patients. In the three trials reviewed, there were two malignant neoplasms in the placebo plus MTX groups and 13 in the CZP groups [42–44]. In combined RA trial data using CZP (n = 2367), there have been a total of three cases of lymphoma, which is twofold higher than the frequency expected in the general population. Congestive heart failure (CHF) has been reported in those using CZP; however, this medication has not been studied

in those with CHF or other cardiac issues. There have been reports of other TNF- α inhibitors worsening CHF. Hypertension has also been observed in those taking CZP compared with those on placebo; however, the hypertensive events were transitory and not related to the study injection [104,42,44].

Antinuclear antibody positivity has been seen in those treated with CZP. Out of the 2367 RA patients given CZP, only four had developed a lupus-like syndrome. Out of a total of 1509 RA patients, 105 (7%) developed antibodies to CZP, with 39 (3%) having neutralizing activity *in vitro*. Patients who were also taking MTX had a lower rate of neutralizing antibody formation [104].

Although there was no alteration of clinical pathology or functional markers, the administration of PEGylated proteins at high doses has been associated with the occurrence of renal tubular vacuolization in animals. It has been demonstrated that PEG associated with a protein or another biological molecule does not pose an additional risk to humans [58,59]. The biological consequence of PEGylation is beyond the scope of this article.

Regulatory affairs

Currently, CZP has been approved for the treatment of moderate to severely active RA by the US FDA [102]. It is also approved in combination with MTX for the treatment of adults with moderate-to-severe RA, or as a monotherapy when there is intolerance to MTX, by Health Canada, the European Commission and the Therapeutic Goods Administration in Australia [103,105,106]. The current recommended dose for RA is 400 mg by subcutaneous injection initially and on weeks 2 and 4. This is followed by 200 mg subcutaneously every other week. In the USA, a 400-mg maintenance dose every 4 weeks can also be used [104].

Conclusion

Certolizumab pegol, one of the newer TNF- α inhibitors, can be administered every other week and has shown to be effective in active RA. The three randomized placebo-controlled trials reviewed here showed significant clinical improvement in those taking CZP, demonstrated by ACR response rates and inhibition of radiographic progression verified by mTSS. Extensions of these trials show sustainability of response. The drug was useful concomitantly with MTX as well as monotherapy in those who failed DMARDs. In these three trials, the drug was generally well tolerated as most AEs were mild to moderate.

Expert commentary

The three major studies reviewed show the benefit of CZP in active RA at a dose of 200 mg every other week with combination MTX as well as monotherapy. There does not seem to be any increased efficacy from administering 400 mg every 2 weeks, and monotherapy with CZP was effective in active RA, albeit at a lower rate. Studies looking at the superiority of MTX plus TNF- α inhibitors versus TNF- α inhibitor monotherapy have shown mixed results. Some showed that combination therapy is superior [11,15,60], while others demonstrated that monotherapy can be as effective [61–63]. The FAST4WARD study did show that CZP monotherapy was effective in treating RA and produces a comparable response to that seen in other TNF- α inhibitor monotherapy trials. This can be a treatment option for those who do not tolerate MTX. There was no comparison of CZP monotherapy to combination CZP + MTX. Therefore, unless there is intolerance, most clinicians would consider continuing a patient on MTX when adding CZP.

The patients enrolled in these trials had active disease despite receiving MTX; however, they were not receiving biologics for at least 6 months prior to CZP administration, which is

similar in design to other TNF- α inhibitor studies. However, this active disease can make response to medication more distinguishable so this should be kept in mind when looking at these data. One can argue that the patients in clinical practice who would be placed on CZP would have refractory disease, which would have been treated with higher doses of MTX and possibly more DMARDs and biologics than the patients enrolled in these three trials.

Two of the trials of CZP had treatment failures withdrawn at week 16. This meant that the number of patients receiving placebo therapy who remained on treatment at week 24 was small and that the placebo response rate was low. A possible reason for this is that many patients will show a response to DMARDs from 16–24 weeks. As a consequence, the benefits of treatment may appear greater with CZP than with other TNF- α inhibitors.

Safety is an important issue when treating with biologic agents. There do not seem to be any major concerns identified from the current data on CZP that are different from other TNF- α inhibitors. TB may be an issue for those at risk and who live in endemic areas. Very few patients have been followed in observational studies of AEs, particularly prospective registries. When compared with the other TNF- α inhibitors, less is known about the relative safety of CZP as there are less long-term data.

As stated previously, the past decade has been revolutionary in terms of research in new RA treatment strategies. It was only a few years ago that clinicians had a choice of three biologics and soon their armamentarium will more than triple. With newer medications being developed, there are some principles that should be remembered prior to their widespread use. Despite the excitement about the biologic era, an emphasis is placed on early use of nonbiologic DMARDs and glucocorticoids when appropriate. The exact time to initiate biologics is not completely clear; however, early aggressive therapy is recommended, therefore patients are to be followed closely with escalation of treatment as needed. This may include combination DMARDs and/or biologic agents. The use of a second- and third-line biologic agent has become standard after one or more therapy has failed. There are patients who do not respond to or have intolerance to certain agents. This is where the newer medications such as CZP play a crucial role in the treatment of RA.

There are no strict guidelines or ways of knowing which biologic or which class to switch to once an individual has failed on one or more. There is a need for a therapy protocol to help clinicians step up treatment; however, this is difficult without head-to-head trials comparing the different agents. At this point, CZP and similar newer biologic agents are options for clinicians and patients. CZP has not completely replaced some of the more traditional biologics but can be used as an alternative treatment as other agents fail, and, in some settings in Europe, it is used as a first-line agent. With a disease such as RA, the more options available, the better the chance of achieving remission. Until there are hard data showing that one biologic is more effective than another, the use of these second- and third-line biologics is at the discretion of the provider.

Five-year view

Certolizumab pegol can be used as monotherapy or concomitantly with MTX, and can accomplish what most other biologics before it have done: improve clinical disease, inhibit radiographic progression and improve the quality of life of those with RA. It does this with a similar AE profile; however, long-term safety data are not available for this drug or some of the newer biologics. The less frequent administration of this agent, as well as of golimumab, could make them more appealing to patients. There are many options for clinicians to turn to when one fails a DMARD and/or biologic. A well-designed head-to-head trial that compares the nine approved biologic agents is currently not available and may never be. Most clinicians will continue to use the traditional biologics (etanercept, infliximab and

adalimumab) after failure of DMARDs such as MTX, until one of these or a newer biologic emerges as a better option.

When the traditional biologics are not effective or a problem with tolerance occurs, there are many approved biologic options and many are in development stages. A current challenge is to discover predictors or biomarkers that designate which individual will respond to a certain DMARD or biologic. Current research on biomarkers may help the clinician to choose a class of drug as first-line therapy and may prove that a biologic is not just the 'next' option for an individual but the optimal choice at a certain time of disease. Biomarkers will be the next step in providing optimal care in a timely manner and may prove that effective first-line agents differ on a case-by-case basis.

With the cost of these biologics being a serious problem for many providers and patients, the hope of knowing which is more effective for a certain individual has many implications for disease and society itself. One must remember the common goal of improving the life of those with RA does not necessarily mean using the newest drug on the market.

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Key issues

- Rheumatoid arthritis (RA), a systemic disease that causes inflammation and joint damage, is treated with disease-modifying antirheumatic drugs (DMARDs) and biologic agents in various combinations.
- Those with persistently active disease after a trial of one DMARD or a combination of DMARDs are usually placed on biologic agents.
- There are currently nine approved biologics in the USA and Europe, with many newer agents in developmental stages.
- Certolizumab pegol (CZP) is a newly approved agent that has shown efficacy with combination methotrexate and as monotherapy in active RA.
- CZP has been shown to be effective in some patients in ameliorating the signs and symptoms of RA, halting the progression of joint destruction and improving quality of life.
- Current data show that CZP is well tolerated; however, long-term safety reports are not available.

Table 1

Current biologics approved by the US FDA and European Commission for the treatment of rheumatoid arthritis.

Drug	Class and structure	Common dose
Etanercept	TNF- α inhibitor Recombinant TNF receptor IgG fusion protein	sc. 50 mg weekly
Infliximab	TNF- α inhibitor Mouse-human monoclonal antibody	iv. 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some may benefit from dosages up to 10 mg/kg as often as every 4 weeks
Adalimumab	TNF- α inhibitor Fully human monoclonal antibody	Sc. 40 mg every other week
Anakinra	Recombinant human IL-1 receptor antagonist	sc. 100 mg daily
Rituximab	CD20-directed cytolytic antio (B-cell depletion) Chimeric human-mouse CD20 agonist	dy iv. Two 1000 mg doses separated by 2 weeks (one course) every 24 weeks
Abatacept	T-cell costimulation modulator Recombinant human CTLA4 Ig fusion protein	iv. 500–1000 mg based on bodyweight Given at 0, 2 and 4 weeks, then every 4 weeks
Certolizumab pegol	TNF- α inhibitor PEGylated Fab' monoclonal antibody	sc. 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week For maintenance dosing, 400 mg every 4 weeks can be considered
Tocilizumab	Humanized anti-IL-6 receptor antibody	iv. 4–8 mg/kg every 4 weeks
Golimumab	TNF- α inhibitor Fully human monoclonal antibody	sc. 50 mg every 4 weeks

iv.: Intravenous; sc.: Subcutaneous.

Table 2

Summary of three key trials showing efficacy of certolizumab pegol in active rheumatoid arthritis.

Study design	Inclusion criteria	Exclusion criteria	Study drugs	Primary outcome(s)	Findings	Ref.
<i>RAPID 1</i>						
Phase III multicenter randomized double-blind placebo-controlled parallel-group 52-week study	Age 18 years RA 6 months but <15 years Active disease [†] Received MTX 6 months, with a stable dosage of 10 mg/week for 2 months prior to baseline	Other inflammatory disease History of TB or positive PPD At high risk of infection Received any biologic 6 months (or anakinra/etanercept 3 months) of baseline History of malignancy, demyelinating disease, blood dyscrasias or other serious illness Prior failure to respond to a TNF inhibitor	n = 393; CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 200 mg every 2 weeks + MTX n = 390; CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 400 mg every 2 weeks + MTX n = 199; placebo + MTX	ACR20 at week 24 (p<0.001) Change in mTSS from baseline at week 52 (p<0.001)	CZP 200 mg: ACR20 at week 24 was 58.8%. Mean change in mTSS at week 52 was 0.4 Sharp units CZP 400 mg: ACR20 at week 24 was 60.8%. Mean change in mTSS at week 52 was 0.2 Sharp units Placebo: ACR20 at week 24 was 13.6%. Mean change in mTSS at week 52 was 2.8 Sharp units	[43]
<i>FAST4WARD</i>						
Multicenter randomized double-blind placebo-controlled 24-week study	Age 18-75 years RA 6 months Active disease+ Failed 1 DMARD DMARDs stopped 28 days prior to study drug or five half lives of the drug, whichever was longer	Other inflammatory disease History of chronic infection History of TB or positive PPD Received any biologic 6 months or prior TNF inhibitor	n = 111; CZP sc. 400 mg every 4 weeks n = 109; placebo	ACR20 at week 24 (p<0.001)	CZP 400 mg: ACR20 at week 24 was 45.5% Placebo: ACR20 at week 24 was 9.3%	[44]
<i>RAPID 2</i>						
Phase III multicenter international randomized double-blind placebo-controlled 24-week study	Age 18 years RA 6 months but <15 years Active disease [†] Received MTX 6 month (stable dose >10 mg/week for >2 months before baseline)	History of TB or positive PPD Received any biologic 6 months or anakinra/etanercept 3 months before enrollings Received previous treatment with a biologic resulting in a severe hypersensitivity or anaphylactic reaction Previously failed to respond to TNF inhibitor	n = 246; CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 200 mg every 2 weeks + MTX n = 246; CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 400 mg every 2 weeks + MTX n = 127; placebo + MTX	ACR20 at week 24 (p<0.001)	CZP 200 mg: ACR20 at week 24 was 57.3% CZP 400 mg: ACR20 at week 24 was 57.6% Placebo: ACR20 at week 24 was 8.7%	[45]

[†] Active disease is defined as at least nine tender and nine swollen joints with either an erythrocyte Sedimentation rate of at least 30 mm/h or C-reactive protein above 1.5 mg/l.

ACR20: American College of Rheumatology Criteria for 20% improvement; CZP: Certolizumab pegol; DMARD: Disease-modifying antirheumatic drug; mTSS: Modified Total Sharp Score; MTX: Methotrexate; PPD: Purified protein derivative; RA: Rheumatoid arthritis; sc.: Subcutaneous.

Table 3

Adverse events and serious adverse events reported in three key trials.

Drug group	Adverse events	Serious adverse events
<i>RAPID 1</i>	<i>Per 100 patient-years</i>	<i>Per 100 patient-years</i>
n = 392 or 303.3 patient years [†] CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 200 mg every 2 weeks + MTX n = 389 or 315.2 patient years [†] CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 400 mg every 2 weeks + MTX n = 199 or 91.4 patient years [†] Placebo + MTX	Any 96.6 Mild 80.4 Mod 57.4 Severe 10.5 Any 94.5 Mild 80.6 Mod 56.2 Severe 12.1 Any 125.9 Mild 98.5 Mod 72.2 Severe 14.2	Any 14.8 Death 0.7 AE leading to withdrawal 5.6 Infections 5.3 Any 15.2 Death 1.3 AE leading to withdrawal 7.0 Serious infections 7.3 Any 12.0 Death 1.1 AE leading to withdrawal 3.3 Serious infections 2.2
<i>FAST4WARD</i>	<i>Number of patients (%)</i>	<i>Number of patients (%)</i>
n = 111 CZP sc. 400 mg every 4 weeks n = 109 Placebo	Any 84 (75.7) Mild 62 (55.9) Mod 52 (46.8) Severe 8 (7.2) Any 63 (57.8) Mild 43 (39.4) Mod 40 (36.7) Severe 11 (10.1)	Any 8 (7.2) Death 0 (0) AE leading to withdrawal 5 (4.5) Serious infections 2 (1.8) Any 3 (2.8) Death 0 (0) AE leading to withdrawal 2 (1.8) Serious infections 0 (0)
<i>RAPID 2</i>	<i>Number of patients (%)</i>	<i>Number of patients (%)</i>
n = 248 CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 200 mg every 2 weeks + MTX n = 246 CZP sc. 400 mg (weeks 0, 2 and 4) followed by CZP 400 mg every 2 weeks + MTX n = 125 [‡] Placebo + MTX	Any 139 (56.0) Mild 108 (43.5) Mod 61 (24.6) Severe 17 (6.9) Any 125 (50.8) Mild 101 (41.1) Mod 57 (23.2) Severe 14 (5.7) Any 66 (52.8) Mild 45 (36.0) Mod 32 (25.6) Severe 5 (4.0)	Any 18 (7.3) Death 1 (0.4) AE leading to withdrawal 12 (4.8) Serious infections 8 (3.2) Any 18 (7.3) Death 1 (0.4) AE leading to withdrawal 7 (2.8) Serious infections 6 (2.4) Any 4 (3.2) Death 0 (0) AE leading to withdrawal 2 (1.6) Serious infections 0 (0)

[†] Mean exposure of study drug longer than placebo so events reported per 100 patient-years.[‡] Two patients in placebo received CZP 200 mg so were included in that group for safety evaluations.

AE: Adverse event; CZP: Certolizumab pegol; Mod: Moderate; MTX: Methotrexate; sc.: Subcutaneous.

Table 4

Adverse events reported by at least 3% of patients in the certolizumab pegol group compared with those taking placebo.

Adverse event	Placebo + MTX (n = 324) (%)	CZP 200 mg [†] +MTX (n = 640) (%)
URI	2	6
Headache	4	5
Hypertension	2	5
Nasopharyngitis	1	5
Back pain	1	4
Pyrexia	2	3
Pharyngitis	1	3
Rash	1	3
Acute bronchitis	1	3
Fatigue	2	3

[†] Certolizumab 200 mg given every other week.

CZP: Certolizumab pegol; MTX: Methotrexate; URI: Upper respiratory tract infection.

Data from [104].