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Drug safety evaluation of certolizumab pegol

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Introduction: The introduction of antibodies directed against tumor necrosis factor (anti-TNF) has dramatically changed our concept of treating both patients with Crohn's disease (CD) and patients with rheumatoid arthritis (RA). Subcutaneous injections with certolizumab pegol (CZP) have been shown efficacious for both CD and RA. In this review, the authors focus on the safety of CZP among other anti-TNF agents.

Areas covered: A literature search till June 2013 was performed to identify all trials studying CZP in patients with CD and RA. In addition, abstracts of major congresses were assessed. The authors first focused on the mechanism of action of CZP, and evaluated the efficacy of this drug in both CD and RA. Next, they explored the available safety data on CZP, including infection and malignancy risk, injection site reactions, the development of antibodies against CZP, as well as its use during pregnancy.

Expert opinion: Based on the provided literature, CZP seems to have a similar safety profile to other anti-TNF agents. However, in young females considering pregnancy, CZP may be advocated over other anti-TNF agents as it does not actively cross the placenta.

Keywords: certolizumab pegol, Crohn's disease, rheumatoid arthritis, safety

Expert Opin. Drug Saf. [Early Online]

1. Introduction

Although the pathogenesis of many immune-mediated inflammatory diseases such as Crohn's disease (CD) and rheumatoid arthritis (RA) remains incompletely unraveled, many studies have shown that tumor necrosis factor (TNF) has a pivotal role in the inflammatory process of these conditions. Consequently, TNF has emerged as an important target, and the introduction of antibodies directed against tumor necrosis factor (anti-TNF) caused a significant advance in the management of both CD and RA [1,2]. Unfortunately, the long-term efficacy of anti-TNF agents may be hampered by several problems, including immunogenicity [3,4]. While many patients initially respond well to anti-TNF agents, some may lose their response or tolerability over time, needing dose optimization or switch to another agent. These issues highlight the need for a wide armamentarium of potent (biologic) anti-inflammatory agents.

In CD, the anti-TNF agents infliximab (IFX, Remicade®, Janssen Biotech Inc., Malvern, PA, USA) and adalimumab (ADA, Humira®, Abbvie Inc., Chicago, IL, USA) are not only able to induce and maintain clinical remission, but also provide the possibility to taper steroids, to rapidly induce and maintain mucosal healing and, on the long-term, to reduce hospitalization and surgery rates [5-14]. Furthermore, maintenance therapy with IFX has also been shown to result in durable fistula healing [15]. Randomized trials with other, non-TNF directed biological agents such as the anti-adhesion molecules and antibodies directed against interleukin (IL)-12 and -23 have shown promising results [16].

In RA, besides IFX and ADA, also etanercept (ETN, Enbrel®, Immunex, Thousand Oaks, CA, USA) and golimumab (GOL, Simponi®, Janssen Biotech Inc.,

10.1517/14740338.2014.851666 © 2013 Informa UK, Ltd. ISSN 1474-0338, e-ISSN 1744-764X

Box 1. Drug summary.

Drug name	Certolizumab pegol
Phase	Launched
Indication	Crohn's disease, Rheumatoid arthritis
Pharmacology description	Antibody fragment and tumour necrosis factor alpha antagonist
Route of administration	Injectable
Chemical structure	Biological protein, antibody Chemical name: Immunoglobulin, anti-(human tumor necrosis factor alpha) Fab' fragment (human-mouse monoclonal CDP870 heavy chain), disulfide with human-mouse monoclonal CDP870 light chain, pegylated
Pivotal trial(s)	[29-36]

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Malvern, PA, USA), have shown efficacy by halting the progression of radiological damage, consequently translated into a slowing or cessation of functional decline [17-25]. In contrast to CD, janus kinase inhibitors and non-TNF directed biological agents are already commonly used in patients with RA, including anti-IL1, anti-IL6 and anti-CD20 antibodies, and antibodies directed against T-cell co-stimulation [26].

Certolizumab pegol (**Box 1**) (CZP, Cimzia®, UCB Pharma, Brussels, Belgium) was the third anti-TNF agent to show efficacy in patients with moderate-to-severe CD, while it is one of the five anti-TNF agents implemented in the treatment of RA. CZP is a PEGylated Fab' fragment of a humanized monoclonal anti-TNF antibody [27]. The presence of polyethylene glycol (PEG) part increases the half-life of the molecule, allowing a subcutaneous injection every 2 or 4 weeks [27].

In patients with RA refractory to disease modifying antirheumatic drugs (DMARDs), four randomized-controlled trials demonstrated efficacy of CZP when used in monotherapy or in combination with methotrexate (MTX) [28-31]. In CD, CZP has been shown efficacious for the induction and maintenance of clinical response in patients with moderate-to-severe disease, but data on (steroid-free) clinical remission, fistula closure and mucosal healing are more limited [32-36].

In this article, we will shortly review the mechanism of action of CZP as well as its efficacy in both CD and RA. Next, we will focus on the available safety data from both the pivotal clinical trials as well as post-marketing data. A literature search till June 2013 was performed to identify all trials studying CZP in patients with CD and RA. In addition, abstracts of major congresses were assessed.

2. Mechanism of action of CZP

CZP is a PEGylated Fab' fragment of a humanized monoclonal anti-TNF antibody (**Figure 1**) [27]. The Fab' fragment is produced in an *Escherichia coli* system [37]. Unlike other monoclonal antibodies, which are based on the human IgG1 Fc, CZP does not contain an Fc portion and, therefore, does not exert Fc-mediated effects. Most recently, the binding affinity of CZP to human Fc receptors was demonstrated to be absent in a Biacore™ assay, IFX (132 nM) and ADA (225 nM) had a relatively high binding affinity which was approximately 5 – 10 fold higher than for ETA (1500 nM) [38]. As a consequence, levels of transcytosis were significantly lower for CZP (3.2 ng/ml), compared to ETA (81.3 ng/ml), ADA (159.5 ng/ml) and IFX (249.6 ng/ml). The PEG was designed to increase the solubility, stability and plasma half-life of the active Fab' fragment reducing the requirement for frequent dosing and, therefore, possibly reducing immunogenicity as well [39]. Furthermore, Fab' fragments are generally regarded less immunogenic than whole antibodies [40]. In animal models, PEGylation of certolizumab favored its distribution into inflamed tissue, an important feature for the effective treatment of medical conditions characterized by chronic inflammation [41,42].

In common with other anti-TNF agents, *in vitro* experiments have demonstrated that the CZP binds soluble and membrane-bound TNF. These analyses have also shown that the CZP has higher binding affinity for TNF than ADA or IFX [27]. Interestingly, in contrast to other anti-TNF agents, CZP did not mediate increased levels of apoptosis in any of the *in vitro* assays. Similarly, due to the absence of an Fc region, CZP does not activate the complement pathway and does not result in cell- or antibody-mediated cytotoxicity. As CZP has been shown efficacious in the treatment of moderate-to-severe CD and RA, apoptosis and cell- or antibody-mediated cytotoxicity may not be required [27,43].

In agreement with IFX and ADA, CZP almost completely inhibited the release of IL-1β from monocytes after induction with lipo-polysaccharide [27]. Additionally, *in vitro* studies on mast cells suggest that the PEG component of CZP can inhibit degranulation response through pathways other than those mediated by immunologic processes [44]. Most recently, German investigators analyzed transcriptomal responses of reversed signaling induced by IFX and CZP in myelomonocytic cells [45]. Both IFX and CZP seemed to modulate non-apoptotic pathways through

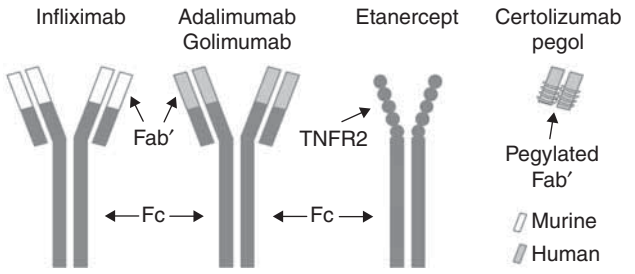

Figure 1. Structure of anti-TNF agents. Infliximab is a chimeric IgG1 monoclonal antibody, whereas adalimumab and golimumab are human IgG1 monoclonal antibodies. Etanercept is a fusion protein of TNFR2 and the Fc region of human IgG1. The humanized certolizumab pegol lacks the Fc portion and the Fab′ fragment is conjugated with polyethylene glycol.

downregulation of pro-inflammatory growth differentiation factor-1 (GDF-1). Further characterization of the molecular role of GDF-1 is mandatory.

For treatment of CD, the CZP is classically administered subcutaneously at a dose of 400 mg, given as two injections of 200 mg each. The induction regimen consists of 400 mg CZP at weeks 0, 2 and 4. The maintenance dose is 400 mg CZP every 4 weeks. In RA, a similar induction and maintenance schedule can be used, but maintenance therapy with 200 mg CZP every other week is more common.

3. Clinical efficacy of CZP in CD

In a dose-ranging Phase II trial, patients with moderate-to-severe CD (Crohn's disease activity index, CDAI between 220 and 450 points) received subcutaneous placebo or CZP at a dose of 100, 200 or 400 mg at weeks 0, 4 and 8 [35]. Although the primary endpoint (a decrease in CDAI of ≥ 100 points or a CDAI of ≤ 150 points for the 400 mg group at week 12) was not achieved, patients randomized to 400 mg CZP achieved clinical response significantly more frequent at all other time points compared to patients randomized to placebo (**Table 1**). At week 10, for example, clinical response was observed in 53% of patients randomized to CZP 400 mg compared to 30% of patients randomized to placebo ($p = 0.006$). Furthermore, in a subgroup analysis of this trial, evaluating only patients with a baseline C-reactive protein (CRP) level of at least 10 mg/l, treatment with CZP 400 mg resulted in a statistically significant benefit at all time-points throughout this 12-week clinical study.

The PRECiSE1 trial evaluated the efficacy of CZP to induce and maintain clinical response in 662 patients with moderate-to-severe CD [32]. Patients were stratified according to baseline concomitant therapy and baseline CRP levels (≥ 10 mg/l or < 10 mg/l) (**Table 1**). Patients were assigned to receive either subcutaneous injections with placebo or CZP 400 mg at weeks 0, 2 and 4 and every 4 weeks thereafter. The primary endpoints were the induction of a clinical response at week 6 (decrease in CDAI of at least 100 points) and the induction of a clinical response at both weeks 6 and 26 in patients with a baseline CRP ≥ 10 mg/l. Among patients with a baseline CRP ≥ 10 mg/l, 37% in the CZP 400 mg group and 26% in the placebo group achieved clinical response at week 6 ($p = 0.04$), while 22 and 12%, respectively, achieved clinical response at both weeks 6 and 26 ($p = 0.05$). In the overall population, clinical response at week 6 was observed in 35% of patients in the CZP 400 mg group compared to 27% in the placebo group ($p = 0.02$).

In PRECiSE2, all 668 patients with moderate-to-severe CD received an open label induction therapy with CZP 400 mg at weeks 0, 2 and 4 [36]. Clinical response at week 6 (decrease in CDAI from baseline with ≥ 100 points) was observed in 64% of patients (**Table 1**). Patients with a clinical response at week 6 were stratified according to their baseline CRP level and were randomly assigned to receive CZP 400 mg or placebo every 4 weeks through week 24. The primary endpoint (clinical response at week 26 in patients with a baseline CRP of at least 10 mg/l) was achieved by 62% of patients randomized to the CZP group compared to 34% in the placebo group ($p < 0.001$). Regardless baseline CRP levels, 63% of all patients randomized to the CZP group compared to 36% of all patients randomized to the placebo group showed clinical response at week 26 ($p < 0.001$).

Patients who completed PRECiSE2 were eligible to enter PRECiSE3 at week 26 (**Table 1**). In this open-label extension trial, CZP 400 mg was administered every 4 weeks for an additional 54 weeks without the option for a dose increase [46]. A total of 141 patients who received CZP (continuous group) and 100 patients who received placebo in PRECiSE2 (drug-interruption group) were enrolled into PRECiSE3. At week 26 (week 0 of PRECiSE3), clinical response rates (decrease in Harvey Bradshaw Index or HBI with ≥ 3 points) for the continuous and drug-interruption groups were 56 and 38%, respectively. Response rates at week 80 in the continuous and drug re-introduction group were 40 and 27%, respectively ($p = 0.005$). However, among patients who were in clinical response at week 26 of PRECiSE2, response rates at week 80 were similar (66 vs 63%, $p = 0.682$).

PRECiSE4 evaluated the outcome of re-introduction of open label CZP in patients participating to PRECiSE2 who relapsed during the double-blind randomized phase (weeks 6 – 26) [47]. Patients who relapsed underwent re-induction with CZP 400 mg at weeks 0, 2 and 4 and every 4 weeks thereafter (**Table 1**). During PRECiSE2, 49 patients in the CZP arm and 75 patients in the placebo arm relapsed and entered PRECiSE4. At week 4 of PRECiSE4, 63% of patients who relapsed on continuous CZP therapy and 65% of patients who relapsed after drug interruption showed a clinical response (decrease in HBI ≥ 3 points). Response was maintained through week 52 in 55 and 59% of these responders, respectively.

Table 1. Clinical efficacy of CZP in CD.

Study [Ref.]	Design	Primary endpoint	Results
Dose-ranging study [35]	Patients with moderate-to-severe CD randomized to placebo or CZP 100, 200 or 400 mg at weeks 0, 4 and 8	A decrease in CDAI of ≥ 100 points or a CDAI of ≤ 150 points at week 12	Primary endpoint achieved by 36% in the placebo group, 37% for CZP 100 mg, 36% for CZP 200 mg, 44% for CZP 400 mg (p = NS)
PRECiSE1 [32]	Patients with moderate-to-severe CD randomized to placebo or CZP 400 mg at weeks 0, 2, 4, and every 4 weeks thereafter	Induction of clinical response (decrease in CDAI of at least 100 points) and the induction of a clinical response at both weeks 6 and 26 in patients with a baseline CRP ≥ 10 mg/l	Clinical response at week 6 was achieved by 26% in the placebo group and 37% in the CZP 400 mg group (p = 0.04) Clinical response at both weeks 6 and 26 was achieved by 12% in the placebo group and 22% in the CZP 400 mg group (p = 0.05)
PRECiSE2 [36]	Patients with moderate-to-severe CD treated with open label CZP 400 mg at weeks 0, 2 and 4 Clinical responders at week 6 were randomized to placebo or CZP 400 mg every 4 weeks	Clinical response at week 26 (decrease in CDAI of at least 100 points) in patients with a baseline CRP of at least 10 mg/l	Clinical response at week 26 was achieved by 34% in the placebo group and 62% in the CZP 400 mg group (p < 0.001)
PRECiSE3 [46]	Open label extension trial for patients with moderate-to-severe CD who completed PRECiSE2 until week 26 CZP 400 mg was administered every 4 weeks for an additional 54 weeks	Clinical response at week 54, defined as a decrease in HBI with at least 3 points	Clinical response at week 80 was achieved by 27% in the drug re-introduction group and 40% in the continuous group (p = 0.005) Among patients with clinical response at week 26, clinical response rates at week 54 were 63% in the drug re-introduction group and 66% in the continuous group (p = 0.682)
PRECiSE4 [47]	Re-introduction of open label CZP at weeks 0, 2, 4 and every 4 weeks thereafter in patients with moderate-to-severe CD who relapsed during PRECiSE2	Clinical response at week 4, defined as a decrease in HBI with at least 3 points	Clinical response at week 4 was achieved by 65% in the re-introduction group and 63% in the continuous group (p = 0.814)
WELCOME [33]	Patients with moderate-to-severe CD who previously failed IFX, received open label CZP 400 mg at weeks 0, 2, 4 Patients in clinical response at week 6 were randomized to CZP 400 mg every 2 or every 4 weeks trough week 24	Clinical response at week 6, defined as a decrease in CDAI with at least 100 points	Clinical response at week 6 was observed in 62% of patients Clinical response at week 26 was achieved by 40% of patients randomized to CZP every 4 weeks and 37% of patients randomized to CZP every 2 weeks (p = 0.546)
Anti-TNF naïve patients [34]	Anti-TNF naïve patients with moderate-to-severe CD, randomized to placebo or CZP 400 mg at weeks 0, 2, 4	Clinical remission at week 6, defined as a CDAI of maximum 150 points	Clinical remission was achieved by 25% of patients randomized to placebo and 32% of patients randomized to CZP (p = 0.174)

Anti-TNF: Antibodies directed against tumor-necrosis-factor; CD: Crohn's disease; CDAI: Crohn's disease activity index; CZP: certolizumab pegol; HBI: Harvey-Bradshaw index; IFX: Infliximab.

In the WELCOME trial, Sandborn *et al.* evaluated the efficacy of open-label CZP 400 mg at weeks 0, 2 and 4 in 539 patients with moderate-to-severe CD (CDAI 200 – 450) who had previously failed IFX [33]. Patients in clinical response at week 6 (decrease in CDAI ≥ 100 points) were randomized to CZP 400 mg every 2 or every 4 weeks trough week 24 (**Table 1**). At week 6, 62% of patients achieved clinical response (primary endpoint) and 39% achieved clinical remission (CDAI ≤ 150 points). A total of 329 patients were randomized and received maintenance therapy with CZP 400 mg every 4 weeks or CZP 400 mg every 2 weeks. At week 26, 40 and 37% of patients in the CZP 400 mg every 4 and every 2 weeks groups, respectively, were in clinical response (p = 0.55). Corresponding remission rates at week 26 were 29 and 30%, respectively (p = 0.81). Besides the fact that CZP every 2 weeks did not demonstrate to be superior, these data showed again that CZP may be a good rescue therapy in patients failing IFX.

Sandborn *et al.* evaluated the efficacy of CZP in anti-TNF naïve patients [34]. In this randomized placebo-controlled trial 439 anti-TNF naïve patients with moderate-to-severe CD received placebo or CZP 400 mg at weeks 0, 2 and 4 (**Table 1**).

The primary endpoint, clinical remission rates at week 6 (CDAI ≤ 150 points), was not significantly different between the CZP and placebo group (32 vs 25%, p = 0.174). Similarly, clinical response rates at week 6 did not differ between the two groups (41 vs 34%, p = 0.179). However, in a subgroup analysis limited to patients with a baseline CRP ≥ 5 mg/l, clinical remission rates at week 6 were significantly higher in the CZP group (p = 0.031). These data highlight the need for an objective evaluation of CD activity prior to initiation of biological therapy.

Data on the role of CZP in mucosal healing are much more limited. In the recent MUSIC trial, Hébuterne *et al.* specifically assessed the efficacy of CZP in improving endoscopic lesions in patients with moderate-to-severe CD [48]. Eighty-nine patients with ulcerations in at least two intestinal segments and with a Crohn's Disease Endoscopic Index of Severity (CDEIS) of at least 8 points were included. Patients received standard induction with open-label CZP 400 mg at weeks 0, 2 and 4 followed by a maintenance schedule with CZP every 4 weeks up to week 52. The mean (± standard deviation) CDEIS score dropped significantly from 14.5 (± 5.3) at baseline to 8.8 (± 6.1) at week 10 and 9.8 (± 6.2) at week 54 (both p < 0.0001). Rates of endoscopic response (decrease in CDEIS score > 5 points), remission (CDEIS score < 6), complete remission (CDEIS score < 3) were 54, 37 and 10%, respectively, at week 10, and 49, 27 and 14% at week 54. However, rates of mucosal healing (absence of ulcerations) at week 10 and week 54 were only 4 and 8%, respectively.

Up to now, no study has been initiated to specifically evaluate the efficacy of CZP for fistulizing CD. The scarce available data are coming from sub-analyses of the PRECiSE studies and a relative small open label cohort study [32,36,49]. In PRECiSE1 and PRECiSE2, complete fistula closure at week 26 was observed in, respectively, 30 and 36% of patients randomized to CZP compared to, respectively, 31 and 17% of patients randomized to placebo (p = 0.920 for PRECiSE1 and p = 0.038 for PRECiSE2) [32,36]. In an open-label Swiss multicenter trial with CZP 400 mg (FACTS), 14 out of 60 patients had perianal fistulizing disease [49]. Complete fistula closure rates were 36% at week 6 and 55% at week 26.

There are currently no published studies in children regarding the efficacy of CZP, but one open label study is currently in progress [50].

4. Clinical efficacy of CZP in RA

The efficacy of CZP was demonstrated in two double-blind, randomized-controlled trials in patients with active RA refractory to MTX therapy (RAPID 1 and 2) [29,30]. In both studies, patients were randomized to subcutaneous CZP 200 mg, CZP 400 mg, or placebo every 2 weeks (**Table 2**). All patients received MTX concomitantly. In patients receiving CZP, a loading dose with CZP 400 mg at weeks 0, 2 and 4 was administered. RAPID 1 was a 52-week trial using a lyophilized subcutaneous CZP formulation, while RAPID 2 was a 24-week trial using a liquid CZP formulation. In both trials, the (co-)primary endpoint was a 20% improvement in the American College of Rheumatology score (ACR20) at week 24.

In RAPID 1, ACR20 was achieved at week 24 by 13.6% of patients randomized to MTX monotherapy, 58.8% of patients randomized to CZP 200 mg every other week plus MTX and 60.8% of patients randomized to CZP 400 mg every other week plus MTX (both p < 0.001 vs MTX monotherapy) [30]. Corresponding ACR20 response rates at week 52 were 13.6, 53.1 and 54.9%, respectively (both p < 0.001 vs MTX monotherapy) (**Table 2**). In RAPID 2, corresponding ACR20 rates at week 24 were 8.7, 57.3 and 57.6%, respectively (both p < 0.001 vs MTX monotherapy) [29]. Clinical and radiographic outcomes were sustained over a 3-year open-label extension period in RAPID 2 [51].

In the randomized-controlled FAST4WARD trial, patients with active RA refractory to one or more DMARDs were randomized to subcutaneous placebo or lyophilized CZP 400 mg every 4 weeks in monotherapy [31]. The primary outcome, ACR20 at week 24, was achieved by 9.3% of patients randomized to placebo and 45.5% of patients randomized to CZP (p < 0.001) (**Table 2**).

In the RA-III study, patients with active RA with inadequate response to MTX were randomized to double-blind therapy with CZP 400 mg or placebo every 4 weeks for 24 weeks in combination with MTX. The primary efficacy end-point, ACR20 at week 24, was achieved by 22.9% of patients randomized to placebo and 45.9% of patients randomized to CZP (p < 0.001) [28].

The 5-year open-label extension data of the FAST4WARD and RA-III study demonstrated a sustained response with CZP [52].

In the REALISTIC and CERTAIN studies, patients with active RA refractory to at least one DMARD were randomized to CZP or placebo while they continued the DMARDs [53,54] (**Table 2**). In the REALISTIC trial, week 12 ACR20 response rates were significantly higher in patients randomized to CZP compared to placebo (51.1 vs 25.9%, p < 0.001) [53]. Interestingly, ACR20 response rates were similar across CZP patients subgroups irrespective of concomitant or previous therapy. In CERTAIN the primary endpoint (clinical disease activity index ≤ 2.8) at both weeks 20 and 24 was 18.8% for CZP and 6.1% for placebo (p = 0.013) [54]. ACR20 response rates at week 24 were 36.5 and 15.3%, respectively (p = 0.001).

Several other trials have demonstrated the efficacy of maintenance therapy with the two recommended CZP regimens (200 mg every 2 weeks or 400 mg every 4 weeks) with or without MTX [55-57].

5. Safety evaluation of CZP regarding infections

In the randomized controlled CD trials, the incidence of adverse events was similar in the CZP and placebo groups, supporting the safety and tolerability of CZP [32-34,36,46,47].

Table 2. Clinical efficacy of CZP in RA.

Study [Ref.]	Design	Primary endpoint	Results
RAPID 1 [30]	Patients with active RA with inadequate response to MTX monotherapy were randomized to MTX every 2 weeks or MTX plus CZP 400 mg at weeks 0, 2 and 4 and 200 mg every 2 weeks thereafter or MTX plus CZP 400 mg at weeks 0, 2 and 4 and 400 mg every 2 weeks thereafter during the 52 week trial	Co-primary endpoints were the ACR20 response rate at week 24 and the mean change from baseline in the radiographic modified total Sharp score at week 52	ACR20 was achieved at week 24 by 13.6% of patients randomized to MTX monotherapy, 58.8% of patients randomized to MTX plus CZP 200 mg every 2 weeks, and 60.8% of patients randomized to MTX plus CZP 400 mg every 2 weeks ($p < 0.001$ for both) The mean change from baseline in modified total Sharp score at week 52 was 2.8 Sharp units for MTX monotherapy, 0.4 Sharp units for MTX plus CZP 200 mg every 2 weeks, and 0.2 Sharp units for MTX plus CZP 400 mg every 2 weeks ($p < 0.001$ for both)
RAPID 2 [29]	Patients with active RA with inadequate response to MTX monotherapy were randomized to MTX every 2 weeks or MTX plus CZP 400 mg at weeks 0, 2 and 4 and 200 mg every 2 weeks thereafter or MTX plus CZP 400 mg at weeks 0, 2 and 4 and 400 mg every 2 weeks thereafter during the 24 week trial	ACR20 response rate at week 24	ACR20 was achieved at week 24 by 8.7% of patients randomized to MTX monotherapy, 57.3 of patients randomized to MTX plus CZP 200 mg every 2 weeks, and 57.6% of patients randomized to MTX plus CZP 400 mg every 2 weeks ($p < 0.001$ for both)
FAST4WARD [53]	Patients with active RA previously failing one or more DMARDs were randomized to receive placebo or monotherapy with CZP 400 mg	ACR20 response rate at week 24	ACR20 was achieved at week 24 by 9.3% of patients randomized to placebo and 45.5% of patients randomized to CZP 400 mg every 4 weeks ($p < 0.001$)
RA-III [28]	Patients with active RA with inadequate response to MTX, were randomized to receive placebo or CZP 400 mg every 4 weeks on top of MTX	ACR20 response rate at week 24	ACR20 was achieved at week 24 by 22.9% of patients randomized to placebo and 45.9% of patients randomized to CZP 400 mg every 4 weeks ($p < 0.001$)
REALISTIC [54]	Patients with active RA previously failing one or more DMARDs were randomized to receive placebo or CZP 400 mg every 4 weeks on top of current DMARDs	ACR20 response rate at week 12	ACR20 was achieved at week 12 by 25.9% of patients randomized to placebo and 51.1% of patients randomized to CZP 200 mg every 4 weeks ($p < 0.001$)
CERTAIN [47]	Patients with low-to-moderate active RA previously failing one or more DMARDs were randomized to placebo or CZP 400 mg at weeks 0, 2 and 4 and CZP 200 mg every 2 weeks thereafter on top of current DMARDs	Percentage of patients in clinical remission at both weeks 20 and 24, defined as a clinical disease activity index ≤ 2.8	Primary endpoint was achieved at both weeks 20 and 24 in 6.1% of patients randomized to placebo and in 18.8% of patients randomized to CZP ($p = 0.013$) ACR20 response rates at week 24 were 15.3% for placebo and 36.5% for CZP ($p = 0.001$)

ACR20: 20% improvement in the American College of Rheumatology score; CZP: Certolizumab pegol; DMARD: Disease modifying anti-rheumatic drug; MTX: Methotrexate; RA: Rheumatoid arthritis.

As with all anti-TNF agents, infections were the most common side effect observed under CZP therapy (**Table 3**) [58]. In the 26-week PRECiSE2 study, serious adverse events and serious infections occurred in, respectively, 6 and 3% of patients in the CZP group compared to 7 and 1% in the placebo group [36]. In the 80-week PRECiSE 3 analysis, similar rates of serious adverse events were reported by patients in the continuous treatment (19%) and drug interruption (17%) groups [46]. Exacerbation of CD was the most commonly reported adverse event.

In the REALISTIC trial, no new safety concerns were raised, and serious adverse event rates (26.7 vs 25.8%) and serious infection rates (11.1 vs 8.3%) were similar between CZP and placebo groups (**Table 3**) [53]. Furthermore, in

Table 3. Safety of CZP.

Infections
Infections (respiratory tract, urinary tract, viral, etc.) are the most common side effect observed under CZP [58]
In randomized controlled trials (serious) infection rates under CZP were not greater than under placebo [36,46,53,59,61]
A Cochrane systematic review suggested higher serious infections rates under CZP compared to other anti-TNF agents [63]
Malignancies
The malignancy and lymphoma incidence ratios are comparable with the background population [58,59]
Development of anti-CZP antibodies
Up to 9% of patients treated with CZP develop anti-CZP antibodies [20-32,35,36,46,51]
Rate of anti-CZP antibodies is lower in patients who receive concomitant immunosuppressive therapy [32,36,46]
Auto-immunity
Up to 17% of patient treated with CZP develop anti-nuclear antibodies [29,58,70]
Up to 2% of patient treated with CZP develop anti-dsDNA antibodies [29,58,70]
Injection site reactions
Up to 7% of patients treated with CZP develop injection site reactions [58]
Miscellaneous
CZP may aggravate heart failure and is contra-indicated in patients with moderate-to-severe heart failure [58]
Hematological adverse events (pancytopenia, thrombocytopenia and anemia) can be observed [58]
Neurological adverse events (multiple sclerosis, optic neuritis, etc.) are rare [58]
Administration during pregnancy
CZP does not actively cross the placenta during pregnancy [71]
CZP in human cord blood levels are much lower compared to levels in mother's blood [71]

CZP: Certolizumab pegol; dsDNA: Double-stranded DNA; TNF: Tumor necrosis factor.

the DOSEFLEX study, reported adverse events rates were similar between the different CZP and placebo groups [57]. Pooled safety data are available for the controlled phases of RA trials as well as for a total of 2367 RA patients treated with open label CZP [59]. In the controlled phase of RA trials, the incidence rate of new infections was 1.03 per patient–year for CZP versus 0.92 per patient–year for placebo, and mainly consisted of respiratory tract infections, urinary tract infections and herpes viral infections [58]. More new cases of serious infections were observed in the CZP group versus the placebo group (0.07 vs 0.02 per patient–year). The most frequent serious infections included pneumonia and tuberculosis. Other serious infections observed were pneumocystosis, fungal esophagitis, nocardiosis and disseminated herpes zoster infection. In 4049 RA patients the incidence of tuberculosis was 0.47 per 100 patient years with most cases reported in countries with a high prevalence for the disease [60]. In the most recent safety update, no new signal has emerged [61]. Of note, patients who receive CZP can be immunized effectively against pneumococcal and influenza infection [62].

A recent Cochrane systematic review, did not demonstrate significant difference with CZP in comparison to other anti-TNF agents in rate of total adverse events. However, CZP was associated with significantly higher odds of serious infections when indirectly compared to other available biological therapies [63]. However, it remains difficult to interpret these data since no head-to-head comparisons are available.

A *post-hoc* analysis of RAPID1 showed that higher baseline steroid use may be associated with a higher incidence of serious infections [64]. This finding is consistent with the results from the British Society for Rheumatology Biologics Register [65]. In CD, the use of steroid also seems to be the main driver of the infection risk [66,67].

6. Safety evaluation of CZP regarding malignancies

Excluding non-melanoma cancer of the skin, 121 malignancies including 5 cases of lymphoma were observed in the CZP RA clinical trials in which a total of 4049 patients were treated. Cases of lymphoma occurred at an incidence rate of 0.05 per 100 patient–years and melanoma at an incidence rate of 0.08 per 100 patient–years [58]. Based on data from 2067 patients treated with CZP, the malignancy and lymphoma standardized incidence ratios (SIR) were 1.22 (95% confidence interval, CI: 0.82 – 1.74) and 4.10 (95% CI: 0.84 – 11.97), respectively (**Table 3**) [59]. However, it remains difficult to interpret the risk of malignancy, since in RA, an increased malignancy/lymphoma risk has been observed in patients with higher levels of disease activity, regardless of anti-TNF use. Furthermore, lymphoproliferative disorders have more frequently been described in patients under thiopurine analogues, which are frequently prescribed in combination with anti-TNF therapy for CD [68]. In the CESAME cohort, the multivariate-adjusted hazard ratio of lymphoproliferative disorders between patients receiving thiopurines and those who had never received thiopurines was 5.28 (CI: 2.01 – 13.9, p = 0.0007). In recent years, the hepatosplenic T-cell lymphoma received a lot of attention, but this remains a very rare (but lethal) condition [69].

7. Safety evaluation of CZP regarding development of anti-CZP antibodies

In the different CD trials, up to 9% of patients randomized to CZP 400 mg developed antibodies against CZP at any time point before week 26, but this was not associated with a decrease in efficacy (**Table 3**) [32,35,36,46]. In the different RA trials, anti-CZP antibodies were observed in up to 8% of patients randomized to CZP [30,31,51]. Of note, in CD a lower incidence of antibody formation was observed in patients who received concomitant immunosuppressive agents or maintenance therapy with CZP [32,36,46]. However, the additive value of concomitant immunosuppressive agents on long-term outcome of CZP therapy is still unknown.

8. Safety evaluation of CZP regarding auto-immunity

In the controlled phase of RA trials, anti-nuclear antibodies and anti-dsDNA antibodies developed in 16.7 and 2.2% of CZP-treated patients, respectively (**Table 3**) [58]. In CD patients randomized in the PRECiSE3 trial, the occurrence of anti-nuclear (6.4%) and anti-dsDNA antibodies (0.6%) was much lower [70]. The impact of long-term treatment with CZP on the development of autoimmune diseases is unknown, but rare cases of lupus-like syndrome have been reported [29,58].

9. Safety evaluation of CZP regarding injection site reactions

In the placebo-controlled RA clinical trials, 5.8% of patients treated with CZP developed injection site reactions such as erythema, itching, hematoma, pain, swelling or bruising, compared to 4.8% of patients receiving placebo (**Table 3**) [58]. Injection site pain was observed in 1.5% of patient. Injections site reactions appear to be lower than with ADA and ETN. *In vitro* studies on mast cells suggest that the PEG component of CZP can inhibit the degranulation response through pathways other than those mediated through immunologic processes [44].

10. Safety evaluation of CZP regarding other adverse events

As for other anti-TNF agents, the use of CZP is contraindicated in patients with moderate-to-severe heart failure (**Table 3**). Case reports are available on new onset of cardiac failure or worsening of cardiac failure with CZP [58]. Further, hematological adverse events (pancytopenia, thrombocytopenia and anemia), as well as neurological adverse event (multiple sclerosis, optic neuritis) have been reported with anti-TNF agents including CZP (**Table 3**) [58].

11. Safety evaluation of CZP during pregnancy

IFX and ADA are IgG1 antibodies which actively cross the placenta through neonatal receptors during the third trimester [71]. As a consequence, we tend to discontinue IFX and ADA around week 20 – 22 of pregnancy. In contrast, CZP does not have an Fc portion and, therefore, does not actively cross the placenta but only passes by passive diffusion. A study on pregnant rats receiving a murinized IgG1 antibody of TNFα (cTN3 γ1) or a PEGylated Fab' anti-rat fragment of this antibody (cTN3 PF), demonstrated much lower drug concentrations in the infant rat with the Fab' fragment compared with the full antibody [72]. In addition to minimal placental transmission with the Fab' fragment, transfer to breast milk was low and fetal absorption negligible. As mentioned previously, levels of transcytosis were significantly lower for CZP compared to the other anti-TNF agents [38].

Similarly, in human the cord blood levels of CZP were only 4% of those in the mother's blood, compared to 160% for IFX and 153% for ADA [71]. Therefore, in females considering pregnancy in the very near future, CZP may be considered the anti-TNF agent of choice given its lack of placental transfer. A recent analysis of mainly post-marketing data on 139 pregnancies after maternal CZP exposure reported 74% live births, 15% miscarriages and 11% elective terminations [73]. These rates are similar to what is expected in the general population. However, additional data from large numbers of pregnant women are required to assess the safety and tolerability of CZP in pregnancy and consequences of *in utero* exposure for the long-term health of the infant.

12. Conclusion

CZP has been shown efficacious in randomized-controlled trials in both patients with CD and in patients with RA. In RA, CZP seems to be as efficacious as the other available anti-TNF agents, whereas the position of CZP in the treatment of CD is more debated.

Although long-term safety data of CZP are lacking, rates of total adverse events are similar compared to other anti-TNF agents. However, data from a Cochrane review suggest a higher rate of serious infections in patients treated with CZP compared to patients treated with other anti-TNF agents. One should take into account that this analysis was based on indirect evidence, not taking into account differences in study design and background risk for adverse events. This highlights the need of head-to-head comparisons.

Most common infectious adverse events include respiratory and urinary tract infections, but serious infections with opportunistic infections have been described. As for other anti-TNF agents, the risk of malignancies (lymphomas in particular), heart failure, neurological and hematological adverse events seems to be increased. The value of combined therapy with

an immunomodulatory agent to avoid immunogenicity towards CZP is still debated. In contrast to other anti-TNF agents, CZP does not actively cross the placenta and could, therefore, be advocated in young females considering pregnancy.

13. Expert opinion

The pivotal randomized-controlled trials with CZP in RA have clearly shown a benefit of CZP over placebo in halting the clinical and radiographic progression of the disease. Based on these data, CZP has been included in the treatment armamentarium for RA among several other anti-TNF antibodies as well as non anti-TNF agents. In CD, however, the position of the CZP in the treatment algorithm is more debated. In some of the pivotal randomized-controlled trials with CZP for CD the primary endpoint was not achieved and subanalyses had to be performed to show significant differences between the use of CZP and placebo. Furthermore, strong endpoints such as steroid-free clinical remission and mucosal healing have hardly been evaluated as primary endpoint in clinical trials with CZP. As a consequence, CZP has not been approved yet for the treatment of CD in most European countries.

The safety issues with CZP are very similar with those observed with other anti-TNF agents. The risk of (severe) infections is higher with CZP than with placebo and the most frequently observed infections are respiratory and urinary tract infections as well as herpes virus infection. The same guidelines regarding prevention of tuberculosis reactivation are used as for other anti-TNF agents. The suggested higher incidence of serious infections compared to other anti-TNF agents is probably due to confounding factors and a head-to-head comparison of different agents is needed to draw any strong conclusion.

Also the risk for malignancies (including lymphomas), heart failure, neurological and hematological adverse events is probably similar among different anti-TNF agents.

Importantly, in contrast to other anti-TNF agents, CZP does not actively cross the placenta and could, therefore, be advocated in young females considering pregnancy.

Declaration of interest

UCB provided abstracts on certolizumab pegol presented at recent conferences. The authors have received speakers fees and grants from UCB and are on the advisory board.

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