Original article

Certolizumab: efficacy and safety profile of a novel pegylated TNF-alpha blocking agent

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Abstract. The treatment of Rheumatoid Arthritis (RA) has changed since the introduction of biological agents. In particular, the anti Tumor Necrosis Factor (TNF)-α molecules have been the first group of drugs showing a good efficacy and safety profile. Among these, a new anti TNF-α antibody has been recently indicated for the treatment of RA: certolizumab pegol (CZP). In the main clinical trials this new pegylated anti TNF-α has shown to be efficacious on clinical, functional and prevention of structural damage in patients with active RA and with inadequate response to traditional disease modifying drugs, including methotrexate. Moreover CZP showed to be well tolerated and most adverse events occurred were mild or moderate. Therefore, results obtained showed that this new molecule can play a role in the treatment of RA. (www.actabiomedica.it)

Key words: certolizumab, anti TNF-α, drugs, rheumatoid arthritis

Introduction

Biological agents have modified significantly the treatment of Rheumatoid Arthritis (RA) in recent years, and anti Tumor Necrosis Factor (TNF)-α drugs have paved the way as the first group of medication indicated for this disease (1). Indeed, many patients respond to these biological agents with an improvement on clinical, function, quality of life and prevention of damage. Recommendations on treating RA to target based on both evidence and expert opinion stated that the treatment aim was defined as remission with low disease activity being an alternative goal in patients with long-standing disease. Remission is an achievable goal and rapid attainment of remission can halt joint damage irrespective of the type of DMARD, synthetic or biological (2).

Thus a tight control with a regular follow-up (every 1-3 months during active disease) with appropriate therapeutic adaptation to reach the desired state within 3 to a maximum of 6 months was recommended. In this context a fast response seems to be important for reaching long-term favorable outcomes.

In RA patients, lack of primary or secondary efficacy to antiTNF-α drugs might lead to the point to switch (among the same class of TNF-α inhibitors) or to swap (change class of biological blockers) medication. Therefore, RA still represents a challenge for the rheumatologist in terms of its optimal management.

Certolizumab pegol (CZP) is a novel pegylated anti-TNF-α, consisting of a Fab' attached to a 40-kDa PEG moiety (Fig. 1).

Attachment of PEG to the Fab' increases the plasma half-life of CZP to ~ 2 weeks, allowing every 2 or 4 weeks, and may contribute to the preferential distribution of the drug to inflamed tissues that has been observed in animal models (3). The novelty of CZP is that the molecule lacks of Fc region, so it does

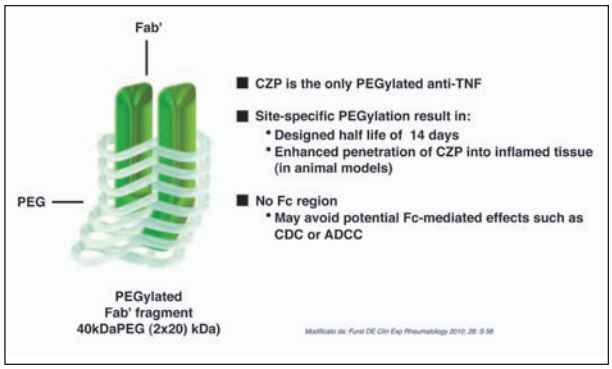

Figure 1. Certolizumab Pegol (CZP)

not induce complement- or antibody-dependent cell-mediated cytotoxicity, which has been seen in vitro with the other molecules such as adalimumab, or infliximab (4)

At present, CZP is approved in the USA, Canada and Europe for the treatment of adult patients with moderate to severe active RA, and in USA and Switzerland for the treatment of patients with Crohn's disease.

Efficacy

The efficacy of CZP has been assessed in three published clinical trials, either in combination with methotrexate (MTX) or as monotherapy. Of note these trials evaluated the efficacy in terms of clinical response, radiological progression of the disease and also on some patient-reported outcomes (PROs), including measure of health related quality of life (HRQoL), physical function, arthritis pain and fatigue. Moreover, the three studies also taken into account some socio-economic aspects such as productivity at work and participation in family, social and leisure activities.

Therefore the following paragraphs will describe the main results of CZP as clinical response and inhibition of radiological progression, either in combination or in monotherapy, and then the results on the main PROs measures as well as the socio-economic aspects considered in these studies.

Certolizumab in combination with methotrexate in RA

The efficacy of CZP was assessed in adult RA patients in three phase III clinical trials, where CZP was administered with MTX or as monotherapy (5-7).

These three studies showed clearly that CZP improved clinical signs and symptoms of active RA, and inhibiting the progression of structural joint damage. The trials also considered some PROs, including HRQoL, function, pain, physical function and household/ work productivity. The efficacy of this new molecule was then assessed by these three pivotal studies with a multi-dimensional approach, looking at objective measures and, also, at the PROs.

Two studies, RAPID1 and RAPID 2, were Phase III trials, multi-centre, randomized, double-blind placebo-controlled evaluating the efficacy and safety of CPZ plus MTX in adults (n=982 and n=619, respectively) with active RA and in treatment with MTX (5, 6). The first study, RAPID1, was a 52-week trial of a lyophilized formulation of CZP, while the second, RAPID2, was a 24-week trial of liquid formulation. The RAPID1 was characterized by a randomization 2: 2: 1 of the two regimens of subcutaneous CZP (400 mg at week 0,2, and 4, followed by 200 or 400 mg) plus MTX. Interestingly this trial contemplates the possibility of an open label-extension study of CZP 400 mg plus MTX every two weeks in patients that at both week 12 and 14 failed to demonstrate an ACR 20 improvement.

Both trials measured as primary efficacy endpoint the proportion of patients achieving a 20% improvement of the ACR response criteria at week 24 (8) (Fig. 2).

The RAPID1 study also considered as co-primary endpoint the radiological progression of the disease measured at week 52 by the mean change from baseline in modified total Sharp score (mTSS). Secondary endpoints were ACR50 and ACR70 response criteria, mean change from baseline of the disease activity status (DAS) assessed in 28 joints and by ESR (DAS-28 ESR). Moreover, as already mentioned before, the PROs were also considered as secondary endpoints. In both trials CPZ showed to be rapid in inducing the relief symptoms and the

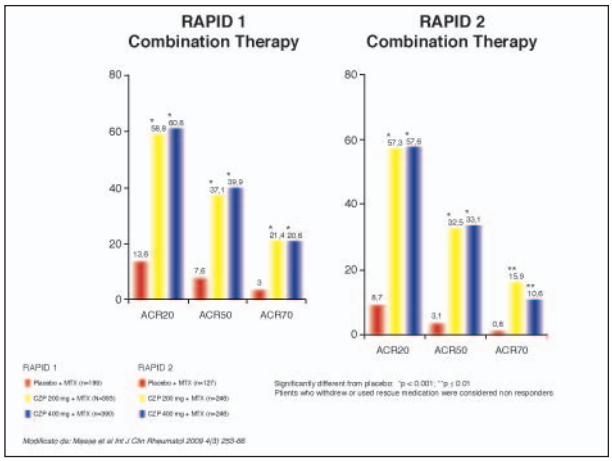

Figure 2. ACR Responder Rates at Week 24 (ITT)

ACR20 response criterion was significantly higher in the group on CZP plus MTX compared to that on placebo (RAPID1: 22.9% in the group on CZP 200mg plus MTX vs 5.6% in those on placebo plus MTX. RAPID2: 14.3% in the group on CZP 200 mg plus MTX vs 3.3% in those on CZP plus MTX (5,6). A good ACR20 response rate was observed at week 12 in both studies (63.8% and 62.7% for CZP 200 mg vs 18.3% and 12.7% for placebo in RAPID1 and 2, respectively; both p<0.001). ACR20 response rate was also high at week 24 with a 58.8% and 57.3% in patients on CZP 200 mg plus MTX, respectively, vs 13.6% and 8.7%.

A higher significant ACR50 and ACR70 response rates were obtained in both studies. In particular, RAPID1 showed at week 2 and week 4 while RAPID2 showed at week 6 and week 20. Moreover, responses were sustained to the end of the two trials, week 52 for RAPID1, and week 24 for RAPID2; interestingly, the response rates obtained were similar in the CPZ 400 mg plus MTX groups. An improvement of all ACR components scores was obtained during the CZP treatment, including the reduction of swollen and tender joint counts and the improvement of both patient's and physician's global assessment of disease activity (5, 6).

In terms of efficacy, measured as improvement of DAS28, the treatment with CZP plus MTX showed a significant improvement from week 1 throughout both trials (5, 6). Mean change of DAS28 (ESR) at week 1 was -0.8 in the group on CZP 200 mg and -0.3 in those on placebo in the RAPID1 study. RAPID2 showed similar results with an improvement of DAS28 (ESR) of -0.8 with CZP 200 mg vs -0.2 with placebo. Of note the improvements were rapid and sustained to the end of both studies and, again were similar in the group treated with CZP 400 mg. DAS28 remission was obtained in 9.4% of the group treated with CZP 200 mg plus MTX compared to those on placebo plus MTX, 0.8%, in the RAPID2 study (6). As mentioned before, both studies measured the efficacy of CZP plus MTX on the progression of joint damage. In RAPID1, the mean change in mTSS from baseline to week 52 was significantly lower in the group of patients on CZP 200 mg plus MTX (0.4±5.7SD) compared to those on placebo plus MTX (2.8±7.8, p<0.001) (Fig. 3-4).

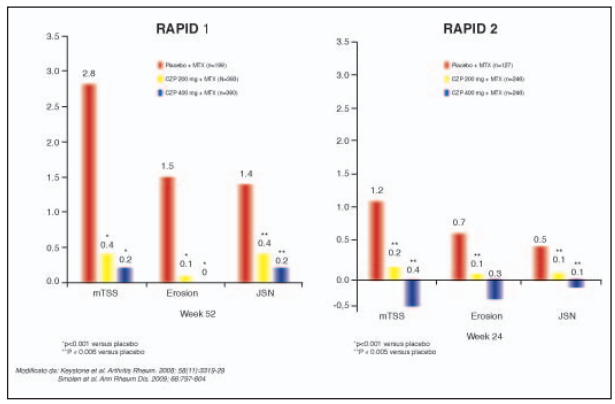

Figure 3. Change From Baseline in mTSS, ES, and JSN

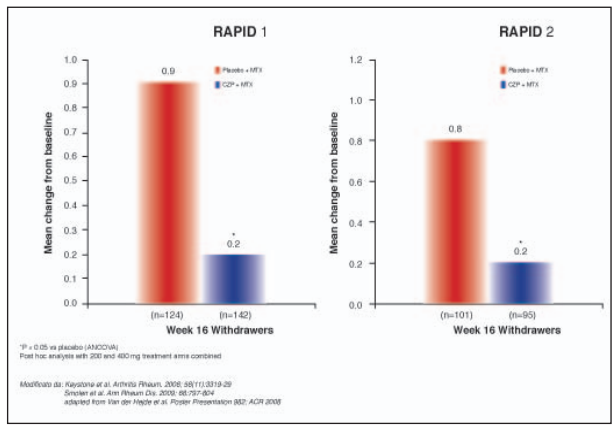

Figure 4. mTSS Mean Change From Baseline at Wk16 (Observed)

At week 24 was also observed a significantly lower progression in the group treated with CZP 200 mg plus MTX, compared to those on placebo. At both time points, the mean changes of erosion were significantly lower in the CZP 200 mg plus MTX compared to those on placebo plus MTX (week 24: 0 vs 0.7; week 52: 0.1 vs 1.5, P<0.001), as well as for the joint space narrowing sub-score (week 24: 0.2 vs 0.7; week 52: 0.4 vs 1.4, p≤0.01). Similar results were obtained in the RAPID2 study: at week 24 the mean change in mTSS from baseline was significantly lower in the group of patients on CZP 200 mg plus MTX (0.2±2.7 SD) compared to those on placebo plus MTX (1.2±4.1 SD, p≤0.01) (6). Similarly to the RAPID1 study, in the group treated with CZP plus MTX in RAPID2 study, a significant lower erosion and joint space narrowing mean change from baseline were observed (0.1 vs 0.7, and 0.1 vs 0.5, respectively, p≤0.01). Of note, similar results were obtained from those patients receiving the 400 mg dosage of CZP. Indeed, the analysis of joint damage in those patients who withdrew from the trials at weeks 16 due to ACR20 non-response at week 12 and 14 (contemplated by the study protocol) found that radiographic progression was inhibited by CZP plus MTX even if the patients did not meet the threshold for a clinical response (5). These findings showed that CZP had a rapid effect and with the possibility to lead to long-terms benefits for patients in terms of slowing the disease progression. Moreover, an ongoing phase III open-label extension (OLE) study to RAPID2 investigating the long-term efficacy and safety of CZP plus MTX over 3 years showed a sustained improvement of signs and symptoms of RA over that period of time and inhibited joint damage progression over 2.5 years (9) (Fig. 5).

A post-hoc analysis of the RAPID1 trial was recently published, aimed to assess the kinetics of response to CZP and the association of a rapid response and longterm outcomes (10). Clinical and radiological outcome measures, assessed at week 52, were evaluated by the DAS28≥1.2 and the ACR20 responses at week 6 and week 12. The analysis showed that patients with a clinical response at week 6 had a faster and more sustained improvement of PROs than those with a good response at week 12. Moreover those patients who achieved a clinical response at week 6 had significantly higher ACR response rates and were more likely to achieve remission at week 52 than those showing a response at week 12. These results, in turn, confirm the efficacy and the fast effect of CZP in active RA.

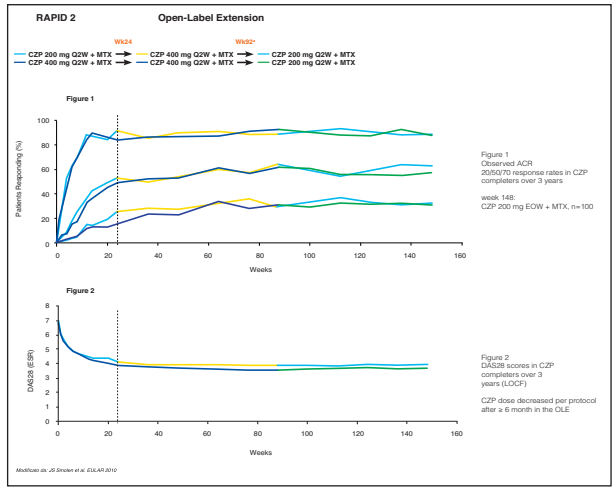

Figure 5. Efficacy and Safety of CZP+MTX: 3 Year Data - Results

Certolizumab as monotherapy in RA

CZP was also administered in mono-therapy trying its efficacy in treatment of RA with a 4-weekly dosage. This third trial, called FAST4WARD, was a phase III, 24-week, multi-centre, randomized, double-blind placebo-controlled trial evaluating its efficacy in 220 adults with active RA who had failed therapy with at least one prior DMARD (7). The study consisted of adult-onset RA who were randomized to receive a lyophilized formulation of CZP 400mg or placebo subcutaneously every 4 weeks. The primary endpoint was ACR20 response at week 24, while radiographic assessments were not performed in this trial. As for the RAPID1 and RAPID2 studies, secondary endpoints included ACR50 and ACR70 responders rates. DAS28 (ESR) and PROs were also taken into account. Even in this trial, patients who completed or withdrew on or after week 12 were offered to entry into an open-label study of CZP 400 mg every 4 weeks, unless they were withdrawn because of non-compliance or possible treatment related adverse events (AEs). Patients enrolled in this study

showed a high disease activity at baseline. The ACR20 response rates were significantly higher in the CZP group compared to the placebo from week 1 (36.7% vs 6.6%, p<0.001) onwards (7). ACR was also significantly higher at week 12, compared to those on placebo and remained constantly higher for CZP until the end of the study. Moreover, ACR50 and ACR70 responses were significantly higher in the group on CZP 400 mg from week 1 and DAS28 (ESR) also showed a greater improvement in the CZP group from week 1 onwards (p<0.001 at all time points) (7).

Effects of CZP on HRQoL, physical function, pain, fatigue and socio-economic aspects

The three studies considered PROs including HRQoL, physical function, arthritis pain and fatigue, as secondary endpoints. HRQoL was measured by using the short-form 36 (SF-36) (11). Fatigue was assessed by using the Fatigue Assessment Scale (FAS), a numerical rating scale (12). Physical function was assessed by using the HAQ-disability index (HAQ-DI) (13, 14). Arthritis pain was assessed by using a 0-to-100-mm visual analogue scale (VAS) (15). The assessment of pain was also considered as daily pain using a modified brief pain inventory (mBPI), which asked patients to rate their worst pain in the past 24 h, average pain in the past 24 h and pain right now.

Then, the proportion of patients achieving minimum clinically important differences (MCIDs) in HRQoL, fatigue, pain and physical function was also considered. For the SF-36 the MCIDs was defined as ≥5.0 point increases from baseline, and for the PCS and MCS as ≥2.5 point increases from baseline (16). The MCIDs for HAQ-DI, pain and FAS were defined as a ≥0.22 point decrease baseline from baseline (17), a ≥10mm reduction from baseline (18) and a 1-point reduction from baseline (19), respectively.

In the studies on the association of CZP and MTX a statistical significant improvement of all SF-36 domains (Physical Component Summary, PCS; Mental Component Summary, MCS) from the initial, week 12 assessment throughout week 52 (RAPID1) and week 24 (RAPID2). Interestingly, the significant improvements observed in RAPID1 and RAPID2 studies at level of SF36-MCS were not previously been seen with other anti TNF-α (20). Similar results were also obtained in the group of patients on CZP 400 mg plus MTX.

The physical function evaluation showed a statistical improvement in the CZP treated patients compared to those on placebo, from the week and continuing with these rapid benefits throughout the two trials. In fact, clinically meaningful improvements of physical function, defined as by improvement greater or equal to MCID, were observed from week 1 in RAPID1 (43% for patients on CZP 200 mg plus MTX vs 25% for those on placebo plus MTX, p<0.001) and from week 2 in RAPID2 (5, 6, 21, 22). The positive trend was constantly throughout the two study until their end (RAPID1 week 52: 47%. RAPID2 week 24: 57%). Finally patients who successfully completed the RAPID1 and entered the open-label extension study of CZP 400 mg plus MTX every two weeks, improvements in HRQoL and physical function and reductions in pain and fatigue were maintained through 100 weeks of treatment at average levels at least three times higher than the threshold for meaningful improvement (23).

Statistically significant improvements in all HRQoL were also obtained during the trial on CZP in monotherapy (7). The SF-36 improved with a statistical significant difference in the group on CZP compared to placebo at week 24 (p<0.001) and the improvements in all SF-36 domains reaching or exceeding the MCID were observed throughout the study. Interestingly, arthritis pain which was assesses daily by mBPI scale during the first week of the FAST4WARD study was significantly reduced compared to those on placebo (p<0.05). Pain assessment, using a pain vas, showed a mean change from baseline of -16.7 vs -5.2 for the CZP and placebo group, respectively (p<0.001). The improvement on physical function was also observed during the FAST4WARD study from the week 1 and throughout the trial, with a statistical significant improvement for the group on CZP (7).

The efficacy of CZP was also measured on some socio-economic aspects, such as the productivity at the workplace and at home. The validated RA-specific Work Productivity Survey (WPS-RA) questionnaire was, therefore, used (24). The survey assessed employ-

ment status, productivity at workplace for those employed and productivity at home and, more in general, daily activities. The trials on the combination of CZP with MTX showed significant improvements on all socio-economic aspects. The group on combination treatment reported less loss of productivity at home compared to those on placebo. The improvement began as early as week 4 when CZP 200mg plus MTX patients reported, as average, fewer household work days missed per month vs placebo plus MTX patients (6.9 vs 7.6, respectively) and this trend was maintained until the end of the studies. A lower rate of RA interference with household work productivity on a 0-10 scale, with 0= no interference and 10=complete interference (5.0 vs 5.9, p≤0.05, RAPID1 study) (25). Moreover, patients receiving CZP plus MTX also reported significant reductions in the number of lost days of family, social and leisure activities due to RA compared to patients receiving placebo plus MTX by week 4 (25). The group of patients on CZP plus MTX showed also an improvement of work productivity (25). In the RAPID1 those patients receiving CZP plus MTX reported an average of 1.5 work days missed per month and 4.3 work days per month with productivity reduced by at least half compared to the group on placebo plus MTX (2.5 and 6.5, respectively; p≤0.05). Finally, a post hoc analysis of these trials found basically that improvements in productivity were in keeping with the improvement in pain, fatigue and physical function. In fact, patients who received improvements reaching the MCID in pain, fatigue and physical function reported also greater improvements in productivity at work and home with also an increased participation in family, social and leisure activities (26).

Safety profile

Updated consensus statement on anti-TNFα drugs for the treatment of RA has established the safety profile on the basis of long-term observations including cohort studies and data from registries (27). Several registries and databases (the majority of the evidence pertains to infliximab, etanercept and adalimumab) have documented an increased risk of serious bacterial infections or tubercolosis with the use of biological DMARDs compared with patients not treated with these drugs (27). Data from US, Canadian, Swedish, German, Spanish and UK Registries have shown no overall increased risk of malignancy (27).

Safety data of CZP are obtained from three pivotal clinical trials: RAPID1(5), RAPID2 (6), FAST4WARD (7).

In RAPID1 (5) and RAPID2 (6), safety analyses were conducted on the population which consisted of all patients who received at least 1 dose of medication (CZP or placebo) plus MTX. Both studies showed that treatment exposure was longer in the CZP arm than in the placebo group. In fact, in RAPID1 the exposure to study treatment, expressed as number of patient-years, was markedly different in 200 mg (n=303.3) and 400 mg (n=315.2) CZP arms than in the placebo arm (n=91.4). For this reason, the authors preferred to present the rates of adverse events (AE) as the number of patients experiencing the event per 100 patient-years or as the incidence rate per 100 patient-years to adjust for differences between CZP and placebo exposure. The overall rates per 100 patient-years of AEs were 125.9 in the placebo group, 96.6 in the 200 mg-CZP group and 94.6 in the 400 mg–CZP group. The infections (mainly urinary tract and upper respiratory tract infections) were comparable between groups and were the most frequent AEs. The most frequent non-infectious AEs were headache (occurring more frequently in patients treated with placebo plus MTX) and hypertension (more common in patients receiving CZP plus MTX). The overall rates per 100 patient-years of serious AEs (SAEs) were similar in the 3 arms (12.0 in the placebo group, 14.8 in the 200 mg-CZP group and 15.2 in the 400 mg-CZP group) with the rates of infectious SAEs in 2.2, in 5.3 and in 7.3, respectively. The rates of infectious SAEs were 2.2, 5.3 and 7.3, in placebo, 200 mg and 400 mg CZP groups. A total of 5 patients (3 of these 5 patients enrolled in East-Europe were PPD positive at baseline) developed tuberculosis after 1.5-9 months of treatment in CZP groups. The rates of AEs that led to withdrawal were 3.3, 5.6, and 7.0 per 100 patient-years in placebo, 200mg and 400mg CZP groups, respectively. The overall rates per 100 patient-years of malignancy were 1.1 in the placebo group, 2.3 in the 200 mg-CZP group and 1.3 in the 400 mg–CZP group.

The incidence of injection site pain and injection site reaction was low both in those taking 200 mg (2% and 2.3%, respectively) or 400 mg (1.3% and 0.8%, respectively) of CZP.

The safety data of RAPID2 are similar to those of RAPID1. AEs occurred in 52.8%, 56.0% and 50.8% of patients in the placebo, 200 mg and 400 mg-CZP groups. The most frequently reported AEs included infections (mainly urinary and upper respiratory tract infection) for placebo (8.8%), for 200 mg-CZP (8.8%) and for 40 mg–CZP (3.7%) group. In this last group hypertension was reported in 3.7% of patients, but post hoc analysis showed that hypertensive events were related to previous hypertensive status, were transitory and were not related to the study injection. The overall rates of SAEs and infectious SAEs were 3.2% and 0% for placebo, 7.3% and 3.2% for the 200 mg-CZP group and 7.2% and 2.4% for the 400 mg-CZP group, respectively. Serious infections included 5 patients with tuberculosis (3 of these 5 patients were PPD positive at baseline) exposed to CZP from 58 to 169 days. We must consider that all patients who developed tubercolosis were enrolled in East-Europe countries, which have high incidence rates of the disease. Moreover, in RAPID2, 101 patients (16%) with a PPD test >5 mm at baseline were enrolled. The rates of AEs that led to withdrawal were 1.6% for placebo and 4.8% and 2.8% for 200 and 400 mg CZP groups, respectively. The overall rates of malignancy were 0.8% in the placebo group and 0.4% in each CZP group. The incidence of injection site pain and injection site reaction was low both in those taking 200 mg (0% and 0.4%, respectively) or 400 mg (1.2% and 2%, respectively) of CZP.

There was no increase in incidence of AEs in the 3 years-open label extension (OLE) of RAPID2, nor were any new safety signals observed (9). In the double-blind and OLE phases combined, SAEs were 13.3 cases/100 patients. The most common SAEs were serious infections (5.46 cases/100 pt-yrs), including tuberculosis (1.29 cases/100 pt-yrs). Overall, AEs led to death in 7 patients treated with CZP plus MTX, 2 in the double-blind phase and 5 in the OLE. Of these 5 deaths, 1 (septic shock) was considered by the study investigator to be possibly related to study drug. The overall rates per 100 patient-years of malignancy were 0.64; there were no lymphomas.

In FAST4WARD study (7), 400 mg-CZP monotherapy, compared with placebo, demonstrated an acceptable safety profile. AEs occurred in 57.8% and 75.7% of patients in the placebo and CZP groups, respectively. The majority of AEs in both treatment groups were mild or moderate and resembling those observed in RAPID1 and RAPID2. The overall rates per 100 patient-years of serious AEs were 9 in the placebo group and 18 in the 400 mg-CZP group. The rates of infectious SAEs were 0 in the placebo group and 4 in the 400 mg-CZP, without any case of tuberculosis. Patients positive for PPD who had received the Bacille Calmette-Guerin vaccination and had a negative chest x ray and no clinical symptoms of tuberculosis could be enrolled in this study, performed in US, Austria and Czech Republic. These results strengthened the relevant role of screening procedure and country origin of patients. The rates of AEs that led to withdrawal were 1.8% for placebo and 4.5% for 400 mg-CZP groups. In FAST4WARD study, benign tumors were reported in 1.8% of patients of CZP group , while no malignancies, including lymphoma, or cases of demyelinating disease were reported. Although no patients in the 400 mg-CZP group reported injection site pain, the rate of injection site reactions in CZP group (4.5%) and placebo (13.8%) of FAST4WARD study was higher than those of RAPID1 and RAPID2, receiving placebo and CZP, respectively.

Laboratory assessment showed that anti–CZP antibodies were detected in 6.4% and in 5.1% (2.6% were neutralising) of patients receiving CZP during RAPID1 and RAPID2, while neutralising antibodies to CZP were detected in 8.1% of patients during monotherapy study (FAST4WARD). In this last study antinuclear autoantibodies titres increased in 17% of patients treated with CZP and in 11% of patients treated with placebo, but no cases of systemic lupus erythematosus (SLE) or SLE-like disease were reported.

A prolonged activated partial thromboplastin time (aPTT) was seen in placebo (1.6%), in the 200 mg (4.8%) and in 400mg (4.9%) dose groups of CZP. These results could be explained by the evidence that PEG interferes with the phospholipid component of some commercial assays that measure aPTT.

Conclusion

The data from the main three studies on CZP showed that this new anti TNF-α agent improves, either in combination with MTX or alone, signs and symptoms of RA with a rapid efficacy, from week 1. Interestingly, the CZP is able to inhibit the radiological progression from week 16, meaning to control the progression of structural damage. Very recently, a post-hoc analysis on the kinetics of response of CZP showed that this new molecule is acting rapidly and the clinical response achieved at week 6 was a good predictor of remission at week 52.

Moreover, controlled and OLE study showed that combination or monotherapy with CZP was well tolerated with a low rate of injection-site reactions and a safety profile similar to that of other anti-TNF therapies.

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