ORIGINAL ARTICLE

**RENACER study: Assessment of 12-month efficacy and safety of 168 certolizumab PEGol rheumatoid arthritis-treated patients from a Spanish multicenter national database**

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**Abstract**

**Objective:** To assess effectiveness and safety of certolizumab PEGol (CZP) in rheumatoid arthritis (RA) patients after 12 months of treatment and to detect predictors of response.

**Methods:** Observational longitudinal prospective study of RA patients from 35 sites in Spain. Variables (baseline, 3- and 12-month assessment): sociodemographics, previous Disease Modifying Anti-Rheumatic Drug (DMARD) and previous Biological Therapies (BT) use; TJC, SJC, ESR, CRP, DAS28, SDAI. Response variables: TJC, SJC, CRP, ESR, and steroids dose reductions, EULAR Moderate/Good Response, SDAI response and remission, DAS28 remission. Safety variables: discontinuation due to side-effects. Descriptive, comparative and Logistic regression analyses were performed.

**Results:** We included 168 patients: 79.2% women, mean age 54.5 years (±13.2 SD), mean disease duration 7.5 years (±7.3 SD). Mean number of prior DMARD: 1.4 (±1.2 SD), mean number of prior BT was 0.8 (±1.1). Mean time on CZP was 9.8 months (±3.4 SD). A total of 71.4% were receiving CZP at 12-month assessment. Baseline predictors of response: lower prior number of DMARD; low number prior BT; higher CRP, ESR, TJC, SJC, DAS28 and SDAI (p < 0.05) scores.

**Keywords**

Certolizumab PEGol, Clinical practice, Efficacy, Rheumatoid arthritis, Safety, Spanish population, Survival rate

**History**

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A 25/46.4% Moderate/Good Response, a 20% SDAI remission, and a 44% DAS28 remission were observed. We observed 48 discontinuations (28.6%), 31 due to partial or complete ineffectiveness, and 17 due to side-effects.

Conclusions: CZP showed benefit in severe RA patients, with significant reduction of all effectiveness parameters, despite the high prevalence of previous BT exposure in our series. We found CRP, ESR, prior DMARD/BT number, TJC, SJC, DAS28, and SDAI as baseline predictors of response. CZP was mostly well tolerated.

Introduction
Rheumatoid arthritis (RA) is a joint inflammatory disease that leads to joint pain, disability and low quality of life. In Spain, the prevalence of RA is 0.5% (95% CI 0.25–0.85) with an estimated women-to-men ratio of 4:1 [1]. The ultimate goal of RA therapy is to achieve remission or low disease activity. Since their first appearance, anti-tumor necrosis factor alpha drugs (aTNFα) have dramatically improved the treatment of RA. Observational studies (e.g. from clinical registries) are needed to determine the possible differences between the various TNFα inhibitors in terms of their ability to induce satisfactory treatment responses (improvement according to the American College of Rheumatology criteria [an ACR response] [2], European League Against Rheumatology (EULAR) response [3] or clinical remission [4], or Disease Activity Score in 28 joints (DAS28) [5], in real-life settings). A further advantage of using observational studies data to assess real-life effectiveness is that the strict inclusion and exclusion criteria in randomized clinical trials make the results more applicable to routine care [6,7]. Although there is a considerable amount of published data regarding the use of infliximab, etanercept, and adalimumab in clinical practice [2,7,8], there is scant data concerning certolizumab PEGol (CZP) use [9].

Infliximab, etanercept, and adalimumab were the first aTNFα to become commercially available, and have been in use for the last 10 years [10,11]. Golimumab and CZP have been approved in Spain for use in RA since 2011. To date, no specific CZP registries have been compiled.

On the other hand, the use of different aTNFα treatments in clinical trials has significantly shown better effectiveness in combination therapy with methotrexate than in monotherapy. Whether this might also be true in CZP patients in clinical practice has yet to be confirmed.

We performed a prospective study with the following objectives:

(1) To assess effectiveness and safety of CZP in a series of RA patients after 3 and 12 months of treatment;

(2) To assess predictors of CZP 12-month response; and

(3) To compare CZP-monotherapy vs. CZP-methotrexate combination response.

Methods
Patients
A nationwide registry addressing the use of CZP in Spain, the Registro Nacional del uso de CTnilizumab (RENECER) registry, was launched in 2011 to record and monitor patients aged over 18 years old with RA using 1987 ACR criteria [12], who initiated CZP on a standard clinical care basis. The registry encomasses 35 hospital and community-based Rheumatology units throughout Spain. Patients aged >18 years are enrolled after giving their written informed consent, and the registry has been approved by the relevant local ethics committee (Internal Code 13/34).

CZP was used according to the Spanish Society of Rheumatology (SER) guidelines for the use of biological therapies in RA [13], which recommended the use of aTNFα in patients with active RA who have failed to respond to two or more Disease Modifying Anti-Rheumatic Drugs (DMARDs) or methotrexate single failure exceptions.

Design
An observational longitudinal prospective study was conducted. We collected data at 3 months and at 12-month visit in order to assess 1-year effectiveness and safety of CZP in RA patients under a clinical practice setting.

Variables
Patient data were recorded at baseline, 3 and 12 months from CZP onset. A patient completed the study if CZP was withdrawn or if completed the 12-month assessment.

The data collected included age, sex, disease duration, smoking status, time from diagnosis to beginning of treatment with a biological drug, glucocorticoids intake, previous DMARDs, previous Biological Therapies (BTs), 28-joint Disease Activity Score (DAS28), tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR; mm/h), rheumatoid factor (RF), joint pain (using a visual analog scale 0–100), side effects, CZP discontinuation and the reason for it, and discontinuation/tapering of glucocorticoids and DMARDs.

Effectiveness was determined by the reduction on TJC, SJC, DAS28 (remission if ≤2.6) [5], EULAR Response (good response: >1.2 reduction plus total score <3.2; and moderate response: 0.6–1.2 reduction plus total score 3.2–5.1) [3], SDAI Response (reduction of >16 points), and the reduction of steroids dosage, CRP and ESR [14].

Thus, we classified a patient as a CZP ‘responder’ if patient fulfilled at least one the following: reduction of DAS28 >1.2 compared with baseline, good or moderate EULAR response and/or SDAI reduction >16.

Safety variables: discontinuations due to side-effects; side-effects nature and date; severity (life-threatening, death).

Patients lost to follow-up because of CZP discontinuation were included in the final analysis at their 12-month visit with the last observed clinical and biological assessment carried forward (LOCF).

Statistical analysis
A descriptive analysis was performed. Responders and non-responders patients’ baseline data were compared using Chi-square test and Fisher’s exact for qualitative variables, and Mann–Whitney’s U-test for quantitative variables. Longitudinal analysis was performed using the Friedman’s test for quantitative variables and Cochran’s test for the dichotomous variables. A multivariate logistic regression model analysis was performed using Response Criteria as dependent variable. Factors with p value <0.10 in the bivariate analysis as the independents variables. Statistical significance was defined for values p <0.05. All statistical analyses were performed using SPSS version 19.0 (IBM Corporation, Armonk, NY).
Results

Socio-demographics and clinical effectiveness data

A total of 168 patients who received CZP to treat their RA were included. Of these, 79.2% were women; mean age 54.5 years old (±13.2); mean disease duration 7.5 years (±7.3). A total of 70.8% of patients had RF-positive titers and 59.8% had CCP-positive titers. Mean time on CZP was 9.8 months (±3.4 SD). Most patients received induction dose at CZP onset (93.5%).

DMARDs’ failure distribution prior to beginning CZP (25.6% none; 32.1% 1, 42.3% ≥2) is shown in Figure 1. Previous BT distribution [54.2% none (naïve), 28.6% 1, 17.2% ≥2] was: etanercept in 23.8% of cases, adalimumab in 19.0%, infliximab in 16.1%, rituximab in 6.5%, tocilizumab in 5.4%, abatacept in 4.2%, and golimumab in 3.0%. Mean number of prior BT was 0.8 (±1.1). Regarding concomitant treatment at baseline, we found 11.9% of patients used oral steroids, 24.4% DMARDs, 50.0% both DMARDs and steroids (Figure 2 shows DMARDs distribution).

A total of 120 patients (71.4%) were receiving CZP at the 12-month assessment in a real-world clinical setting, as retention rate. Effectiveness variables (Table 1) and steroids use were significantly reduced at 3- and 12-month assessments (Table 2).

Safety

We observed 48 discontinuations (28.6%): 31 due to partial or complete ineffectiveness and 17 due to side-effects: six within the first 3 months of CZP initiation (one of each: varicella zoster reactivation, dry mouth, unexplained fatigue, mild skin rash, pityriasis alba, mild raised liver enzyme test), and 11 at 12 months (one of each: acute infectious otitis, mild raised liver enzyme test, oral aphthosis, dry cough, urticarial rash, hands pustulous–papulous rash, adenoid tuberculosis, pancreatitis, unexplained fatigue, upper respiratory tract mild infection, and acute sinusitis). All led to CZP discontinuation. No life-threatening side-effects and/or deaths were registered.

Predictors of response

After comparing CZP Responders vs. Non-Responders using DAS28/EULAR Response/SDAI in the logistic regression model, we found the following variables as predictors of response: lower number of previous DMARD use; lower number of previous BT exposure; BT-naïve, higher baseline CRP, ESR, TJC, SJC, DAS28, and SDAI (p<0.05) (Supplementary Material). Table 3 shows all baseline predictors of response when adjusting for all variables in the binary logistic regression model.

CZP monotherapy

We explored effectiveness differences regarding the use of CZP in monotherapy vs. combined therapy with MTX, based on prior use of BT. We found better 12-month response in monotherapy CZP-treated patients who had previously failed to only one aTNFα (Table 4).

Discussion

To the best of our knowledge, this is the first registry that specifically addresses CZP effectiveness and safety in a routine clinical practice setting in a 12-month period. CZP provided clear benefits in RA patients who had failed to standard treatments (both DMARD and BT) showing significant improvement in all clinical and serological parameters. These data did not differ from those shown by other aTNFα, such as etanercept and adalimumab in clinical practice setting, higher than previous observations with infliximab [15], and also very similar to the Swedish registry recently published [9]. Even more, our findings were similar to those observed in different clinical trials of CZP, either after DMARD failure or intolerance [16–19] or MTX-naïve [20].

Comparisons to another observational nationwide Swedish registry (SRQ) [9] observations may be performed, but only at 3-month period, as this study assessed clinical CZP effectiveness and safety at 3- and 6-month period from its onset. It must be said that patients might not be completely comparable, as at baseline, our patients showed higher mean DAS28 score than SRQ patients.

Table 1. Clinical effectiveness data at baseline, 3- and 12-month assessments.

|                | Baseline | 3 months | 12 months | p value |
|----------------|----------|----------|-----------|---------|
| TJC            | 8.0 (±5.2)| 4.7 (±5.3)| 3.3 (±5.2)| <0.001  |
| SJC            | 6.0 (±4.5)| 3.1 (±4.2)| 2.2 (±3.9)| <0.001  |
| CRP            | 9.0 (±12.7)| 5.7 (±11.7)| 4.7 (±9.9)| <0.001  |
| ESR            | 32.3 (±25.3)| 25.7 (±21.2)| 23.5 (±19.9)| <0.001  |
| DAS28          | 5.1 (±1.3)| 4.0 (±1.6)| 3.4 (±1.7)| <0.001  |
| DAS28 remission| 7 (4.2%)| 40 (23.8%)| 74 (44.0%)| <0.001  |
| EULAR moderate/good response | 33 (19.6%)/50 (29.8%)| 42 (25.0%)/78 (46.4%)| <0.001  |
| SDAI           | 35.8 (±18.1)| 22.1 (±20.7)| 17.1 (±19.6)| <0.001  |
| SDAI remission | –        | 9 (5.6%)| 32 (20.0%)| <0.001  |

Data are shown as: number (%) and mean (±standard deviation).
(5.1 ± 1.3 vs. 4.6 ± 1.4, respectively). The outcome parameters are very similar, although we found slightly lower overall 3-month EULAR response rate compared with the SRQ patients (48.4% vs. 58.2%, respectively). However, the rate of Good EULAR responders was higher in our study (29.8% vs. 23.9%, respectively). Noteworthy, we found response rates were higher as longer was the follow-up (12-month), while SRQ found very similar response rates between 3- and 6-month period assessments. The survival-on-drug in the SRQ study was assessed up to 30-month follow-up, and it seemed comparable with other aTNFα observational registries. The authors found it higher in those who were taken concomitant MTX and who had high disease activity at baseline, and lower in patients with more previous failure to an aTNFα.

The DANBIO registry showed a similar clinical response rate at 12 months for etanercept (32/49% EULAR Moderate/Good Response 32/49 and 33% DAS28 remission), adalimumab (30/57 and 39%, respectively) and infliximab (39/40 and 27%, respectively), compared with our CZP (25/46 and 44%, respectively) observations. In all of these previous studies concomitant treatment use with steroids, MTX or both was even higher than what we observed with CZP. For example, in the DANBIO registry, infliximab was combined with MTX and steroids in 87 and 50% of patients, respectively. In addition, steroids were significantly reduced after 3 and 12 months of CZP treatment compared with baseline. The use of steroids at baseline in all published data varies from 29 to 84% [11,21–23]. In our series we also observed a high rate of steroid use (over 60% with a mean daily dosage of 8.8 mg). However, CZP significantly reduced both the proportion of patients on steroids and the mean daily dosage. The latter assessment was not performed in the SRQ study [9].

The retention rate for CZP use was similar to those observed with other aTNFα drugs in other series [6,16–18], although no direct comparisons could be made for the aforementioned reasons. Nevertheless, as previously described, retention rates for etanercept, infliximab, and adalimumab can vary from 70 to 84% after the first year [21]. No specific data on overall 12-month retention rate are shown in SRQ study [9].

In comparisons with other aTNFα series, we observed a very similar or slightly lower side-effects occurrence rate than what had been recorded in other 12-month follow-up series: the prevalence in an adalimumab registry ranged from 12 to 32% [24–26]. Flouri et al. [27] found that adalimumab showed a 4.1%, etanercept a 1.0% and infliximab a 6.1% rate of discontinuations due to side-effects; a Hellenic registry found an 8.5, 5.3, and 3.5 incidence rate per 100 persons of side-effects with infliximab, adalimumab, and etanercept, respectively [28]. However, no specific data for each aTNFα within the first year were described. In addition, of all the serious infections recorded during the 5-year-follow-up, 42% occurred in the first 12 months from BT onset. Serious aTNFα-related infections have been linked to older age, the concomitant use of prednisolone and DMARD, and the use of infliximab or adalimumab vs. etanercept [29]. No serious infections were observed during the 12-month CZP treatment course. The different designs underlying all these studies precluded any possibility of making direct comparisons. In the SRQ study, patients on CZP showed a total of 15.2% discontinuations in a 30-month period due to intolerance or non-inefficacy related decisions [9].

Among the variables that impacted the 12-month response, we found the as predictors of response the higher CRP and ESR levels, the lower number of both previous DMARDs and BTs use, and the higher TJC, SJC, DAS28, and SDAI scores. After adjusting for all these factors, we determined that only previous lower DMARDs use and both higher baseline SJC and DAS28 served as significant response predictors (OR ranging from 1.3 to 1.8). The SRQ study also showed more benefit in terms of clinical improvement in those patients with higher baseline disease activity (as mean DAS28 score), although higher remission rates were achieved in those patients with non-high DAS28 (≤5.1) compared with those with high baseline DAS28 (>5.1) [9].

As has been previously described, concomitant MTX might be a positive predictor of a good aTNFα response [25,30,31], although other authors have not confirmed this [6]. In fact, we did not find MTX to be an effective predictor of response. For example, the use of CZP in monotherapy did not show lower clinical response rates. Concomitant DMARD influence on the latter was not assessed in the SRQ study [9].

Unlike other studies, we did not find any differences regarding RA duration as a response predictor [12]. Unfortunately, we did not specifically assess anti-CZP antibodies.

As previously described, we did not find differences in terms of clinical response among patients who were active smokers. Recent works from large European registries have suggested that smokers and past smokers are at higher risk of showing poorer response to aTNFα than non-smokers [30,32,33]. No data about CZP response based on smoking status was communicated in the SRQ study [9].

We observed that the use of CZP in monotherapy (23% of patients) did not result in poorer response rates than those involving concomitant MTX. No data on CZP monotherapy was shown in the SRQ study [9]. Moreover, we observed better response in patients treated with CZP in monotherapy after failing.

Table 2. Steroids use and dosage throughout CZP use in RA patients.

|                      | Baseline | 3 months | 12 months | p value |
|----------------------|----------|----------|-----------|---------|
| Glucocorticoids use  | 104 (61.9%) | 88 (52.4%) | 78 (46.4%) | <0.001  |
| Glucocorticoids (mg dosage) | 8.8 (±6.9) | 6.6 (±5.7) | 4.8 (±5.2) | <0.001  |

Data are shown as: (%) and Mean (±SD).

Table 3. Binary logistic regression model results.

|                      | OR       | IC95% (OR) | p value |
|----------------------|----------|------------|---------|
| Using DAS28 response criteria |          |            |         |
| Higher Baseline DAS28 | 1.844    | 1.37:2.48  | <0.001  |
| Lower number of previous DMARD use | 1.406    | 1.03:1.92  | 0.031   |
| BT-naïve             | 1.949    | 0.97:3.93  | 0.061   |
| Using EULAR response criteria |          |            |         |
| Lower number of previous DMARD use | 1.362    | 1.01:1.85  | 0.048   |
| Higher SJC           | 1.312    | 1.17:1.47  | <0.001  |
Table 4. Certolizumab PEG effectiveness response in monotherapy according to the different response criteria used and prior administration of aTNFα, compared with combined therapy with methotrexate.

| Visit | Bio-naïve | MTX (+) | MTX (−) | p value | OR (IC 95%) |
|-------|-----------|---------|---------|---------|-------------|
|       | Total     | MTX (+) | MTX (−) |         |             |
|       |            | OR (IC 95%) | OR (IC 95%) |          |             |
|       |            | p value | p value |     |             |
|       | Total MTX (+) |     |     |       |             |
|       | MTX (−) | OR (IC 95%) | OR (IC 95%) |          |             |
|       | p value |             |             |            |             |
|       | OR (IC 95%) |             |             |          |             |
|       | p value |             |             |            |             |
|       | OR (IC 95%) |             |             |          |             |
|       | p value |             |             |            |             |
|       | OR (IC 95%) |             |             |          |             |
|       | p value |             |             |            |             |
|       | OR (IC 95%) |             |             |          |             |
|       | p value |             |             |            |             |
|       | OR (IC 95%) |             |             |          |             |
|       | p value |             |             |            |             |
|       | OR (IC 95%) |             |             |          |             |
|       | p value |             |             |            |             |
|       | OR (IC 95%) |             |             |          |             |

- **DAS28**
  - **Criteria:** Responders
  - **3 m:** 50 (54.9%) 30 (53.6%) 20 (57.1%) 0.739 0.865 (0.37; 2.03) 15 (31.3%) 7 (29.2%) 8 (33.3%) 0.755 0.824 (0.24; 2.79) 6 (20.7%) 2 (15.4%) 4 (25.0%) 0.663 0.546 (0.08; 3.58)
  - **12 m:** 64 (70.3%) 40 (71.4%) 24 (68.6%) 0.772 1.146 (0.46; 2.87) 25 (52.1%) 11 (45.8%) 14 (58.3%) 0.386 0.604 (0.19; 1.89) 13 (44.8%) 5 (38.5%) 8 (33.3%) 0.711 0.625 (0.26; 1.58)

- **EULAR Responders**
  - **3 m:** 54 (59.3%) 34 (60.7%) 20 (57.1%) 0.736 1.159 (0.49; 2.73) 20 (41.4%) 8 (33.3%) 12 (50.0%) 0.242 0.500 (0.16; 1.61) 9 (31.0%) 4 (30.8%) 5 (31.3%) 1.000 0.977 (0.20; 4.70)
  - **12 m:** 71 (78.0%) 45 (80.4%) 26 (74.3%) 0.496 1.416 (0.52; 3.86) 33 (68.8%) 16 (66.7%) 17 (70.8%) 0.043 0.300 (0.06; 0.88) 16 (55.2%) 8 (61.5%) 8 (33.3%) 0.663 0.546 (0.08; 3.58)

- **SDAI Responders**
  - **3 m:** 38 (45.8%) 20 (41.7%) 18 (51.4%) 0.772 1.146 (0.46; 2.87) 15 (31.3%) 7 (29.2%) 8 (33.3%) 0.755 0.824 (0.24; 2.79) 6 (20.7%) 2 (15.4%) 4 (25.0%) 0.663 0.546 (0.08; 3.58)
  - **12 m:** 48 (57.8%) 28 (58.3%) 20 (57.1%) 0.914 1.050 (0.43; 2.54) 25 (52.1%) 9 (37.5%) 16 (66.7%) 0.386 0.604 (0.19; 1.89) 13 (44.8%) 5 (38.5%) 8 (33.3%) 0.711 0.625 (0.26; 1.58)

- **Number of patients (percentage %).**

**Bold indicates statistical significant value.**

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Certolizumab in rheumatoid arthritis patients

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