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ORIGINAL RESEARCH

Exploring the influence of baseline rheumatoid factor levels on TNF inhibitor retention rate in patients with rheumatoid arthritis: a multicentre and retrospective study

Clementina López-Medina ,[1,2,3] Jerusalem Calvo-Gutiérrez,[1,2,3] M Carmen Ábalos-Aguilera,[2,3] Francisco Cepas,[3] Chamaida Plasencia-Rodríguez ,[4,5] Ana Martínez-Feito ,[4,5] Alejandro Balsa ,[4,5] Regina Faré-García,[6] Antoni Juan-Mas,[6] Virginia Ruiz-Esquide,[7] Luis Sainz,[8] César Díaz-Torné,[8] Francisco Javier Godoy-Navarrete,[9] Isabel Añón-Oñate,[9] Natalia Mena-Vázquez ,[10,11] Sara Manrique-Arija ,[10,11,12] Marina Soledad Moreno-García,[13] Rafaela Ortega-Castro,[1,2,3] Alejandro Escudero-Contreras[1,2,3]

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For numbered affiliations see end of article.

Correspondence to
Dr Clementina López-Medina; clementinalopezmedina@gmail.com

ABSTRACT

Objective To assess whether the retention rate of certolizumab pegol (CZP) was longer than that of other tumour necrosis factor inhibitors (TNFi) based on baseline rheumatoid factor (RF) levels.

Methods Longitudinal, retrospective and multicentre study including patients with RA who were treated with any TNFi (monoclonal antibodies (mAB), etanercept (ETA) or CZP). Log-rank test and Cox regressions were conducted to evaluate the retention rate in the three groups according to the level of RF, with the third quartile of the baseline levels used as cut-off: <200 (<Q3) and ≥200 (≥Q3) IU/mL. A sensitivity analysis matching patients using a propensity score technique based on age, concomitant use of methotrexate and previous targeted synthetic/biological disease-modifying antirheumatic drugs was performed to address the imbalance across groups.

Results A total of 638 individuals and 752 treatments (132 CZP, 439 mAB and 181 ETA) were included. In non-naïve patients with ≥200 IU/mL of RF, those treated with CZP showed a significantly longer retention rate in comparison with mAB and ETA. After matching using the propensity score, patients with ≥200 IU/mL RF levels exhibited longer retention rates with CZP than with mAB (HR 2.3 (95% CI 1.2 to 4.3), or ETA (HR 2.8 (95% CI 1.5 to 5.2). No differences were found between groups in patients with <200 UI/mL.

Conclusions CZP showed a longer retention rate than mAB and ETA in patients with very high RF levels (≥200 IU/mL), while these differences were absent in patients with <200 IU/mL levels. The results suggest the potential effect of RF on binding the fragment crystallisable portion of certain TNFi.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It has been demonstrated that rheumatoid factor (RF) can bind to the fragment crystallisable (Fc) of certain monoclonal antibodies, leading to a reduction in drug levels.

⇒ Conversely, drugs lacking the Fc fragment, such as certolizumab (CZP), have exhibited optimal drug levels in patients with rheumatoid arthritis (RA) and high RF levels compared with other tumour necrosis factor (TNF) inhibitors (TNFi).

⇒ Thus, CZP may show a potentially longer retention rate than TNFi drugs with Fc in patients with RA with high RF levels.

WHAT THIS STUDY ADDS

⇒ Patients with ≥200 IU/mL of RF exhibited longer retention rates with CZP than with monoclonal antibodies and etanercept irrespective of age, the concomitant use of methotrexate and their treatment history (naïve or non-naïve).

⇒ These findings reinforce the hypothesis of the potential role of RF in binding the Fc fragment (which is absent in CZP) and in neutralising the effect of TNFi that contains an Fc portion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results support the suitability of the use of CZP in patients with elevated RF levels, as they seem to show a lower likelihood of treatment discontinuation.

Table 1 Baseline characteristics of the included population

	Overall population N=752 Mean (SD)	CZP N=132 Mean (SD)	mAB N=439 Mean (SD)	ETA N=181 Mean (SD)	P value
Sex (female), n (%)	608 (80.9)	113 (85.6)	348 (79.3)	147 (81.2)	0.266
Age*	53.0 (12.2)	49.1 (12.8)	55.1 (11.6)	50.7 (11.8)	<0.001
Diagnosis delay (years)*	1.2 (2.7)	0.6 (1.8)	1.4 (2.9)	1.1 (2.6)	0.069
Disease duration (years)*	4.7 (7.8)	2.5 (4.8)	5.6 (8.2)	4.3 (8.0)	0.008
Rheumatoid factor positive, n (%)	558 (74.2)	99 (75.0)	328 (74.7)	131 (72.3	0.811
Rheumatoid factor levels (IU/mL)	207.1 (648.0)	247.4 (422.6)	191.0 (649.5)	216.7 (770.3)	0.664
ACPA positive, n (%)	362/448 (80.8)	79/99 (79.8)	190/232 (81.9)	93/117 (79.5)	0.830
DAS28*	4.89 (1.16)	4.88 (1.25)	4.81 (1.18)	5.05 (1.05)	0.208
Concomitant methotrexate, n (%)	452/749 (60.3)	59/131 (45.0)	276/437 (63.2)	117 (64.6)	<0.001
≥1 previous ts/bDMARD, n (%)	218/744 (29.3)	51/130 (39.2)	120/434 (27.6)	47/180 (26.1)	0.022

*Available data for continuous variables: Age n=751, diagnosis delay, n=501; disease duration, n=511; DAS28, n=433.
ACPA, anti-citrullinated protein autoantibodies ; CZP, certolizumab pegol; DAS28, Disease Activity Score 28; ETA, etanercept; mAB, monoclonal antibodies (infliximab, adalimumab and golimumab); ts/bDMARD, targeted synthetics / biological disease-modifying antirheumatic drugs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterised by polyarthritis, joint damage and functional disability. An important component associated with RA is the presence of rheumatoid factor (RF), which is an autoantibody that targets the fragment crystallisable (Fc) portion of IgG, thus forming immune complexes that play a significant role in the development of RA. Notably, approximately 80% of patients with RA have detectable levels of RF antibodies. RF antibodies found in patients with RA exhibit extensive somatic mutations, leading to increased antigen-binding affinity and specificity for IgG[1] and contributing to the perpetuation and progression of the disease.

Tumour necrosis factor inhibitors (TNFi) represent the most widely used biological disease-modifying antirheumatic drugs (bDMARDs) in clinical practice for patients with RA. To date, five TNFi have been approved as a treatment for patients with RA: infliximab (IFX), etanercept (ETA), adalimumab (ADA), golimumab (GOL) and certolizumab pegol (CZP). These drugs, however, possess distinct structural characteristics. IFX, ADA and GOL are classified as fully functional IgG1 monoclonal antibodies against TNF and encompass the immunoglobulin Fc portion. In contrast, ETA functions as a soluble receptor against TNF that is fused with the Fc portion of human IgG1. Among these, CZP stands out as the sole TNFi without an immunoglobulin Fc portion in its structure. CZP is a monovalent Fab fragment that targets TNF and is fused with polyethylene glycol.[2]

It has been demonstrated that RF can bind to the Fc fragment of IFX,[3] resulting in decreased drug levels. This finding leads us to hypothesise that RF might also interact with the Fc portion of other TNFi and influence their clinical efficacy. Conversely, drugs without the Fc fragment, such as CZP, could potentially exhibit improved efficacy and longer retention rates in patients with RA with high RF levels compared with other TNFi drugs. Indeed, an in vivo study supported this hypothesis by showing that patients with RA with high baseline RF levels experienced lower levels of IFX and ADA after 6 months of follow-up, while CZP levels remained stable regardless of RF levels.[4] Furthermore, a recent study provided additional evidence in favour of TNFi drugs without the Fc fragment, such as CZP, being potentially more effective than TNFi drugs with Fc in patients with RA with high RF levels.[5]

Based on the information presented above, the primary objective of this study was to assess whether the retention rate of CZP (a surrogate marker of clinical effectiveness and safety) was longer than that of other TNFi based on the baseline RF levels and according to the previous use of targeted synthetic (ts-) or bDMARDs. In addition, we completed the analysis using propensity score matching to overcome the potential imbalance of baseline characteristics across treatment groups.

METHODS

Study design and population

This is a longitudinal, retrospective and multicentre study involving eight participating centres from Spain. The study included patients diagnosed with RA by their treating rheumatologist in accordance with the 2010 American College of Rheumatology classification criteria.[6] The inclusion criteria encompass individuals who have been treated with any TNFi between 2010 and 2022. This selected time frame was purposefully chosen because it corresponds to the period during which all five TNFi medications were available for clinical use (online supplemental figure 1).

Variables

The main outcome was to assess the retention rate of the different drugs by analysing both the initiation and

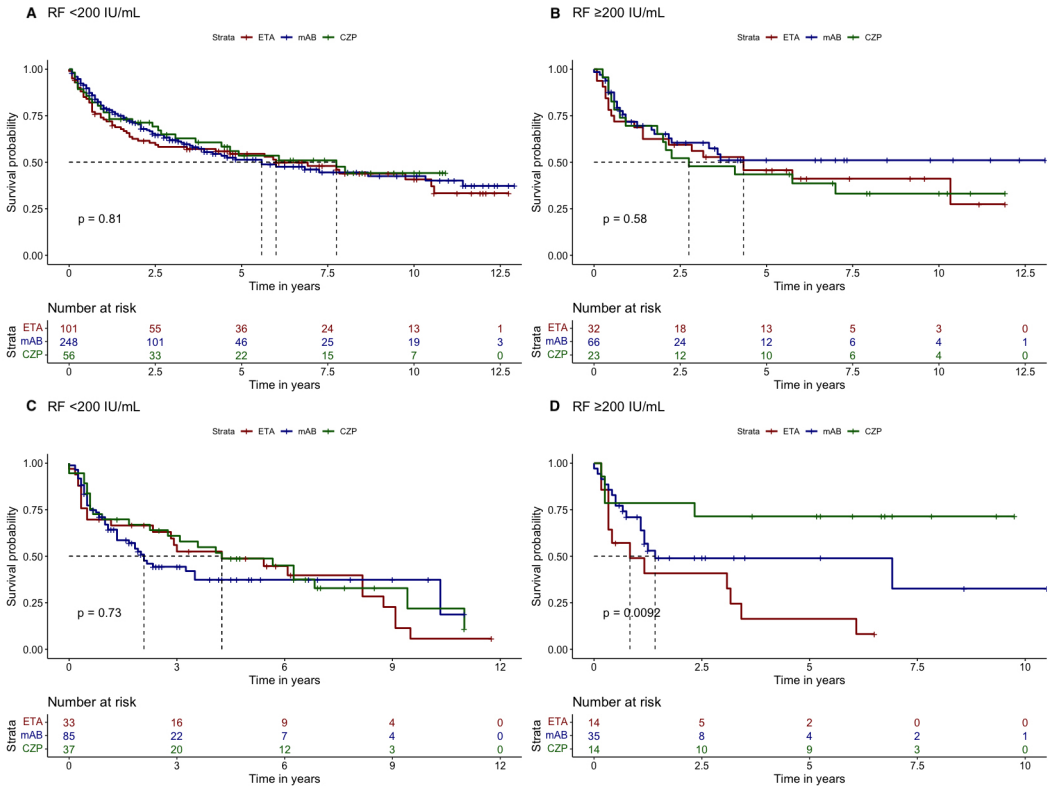

Figure 1 Retention rate of the three treatments in naïve and non-naïve patients regarding the baseline levels of rheumatoid factor. Analysis in (A) naïve patients with rheumatoid factor <200 IU/mL; (B) naïve patients with rheumatoid factor ≥200 IU/mL (very high levels); (C) non-naïve patients with rheumatoid factor <200 IU/mL; (D) non-naïve patients with rheumatoid factor ≥200 IU/mL (very high levels); ie, adalimumab, infliximab and golimumab). CZP, certolizumab pegol; ETA, etanercept; mAB, monoclonal antibodies; RF, rheumatoid factor.

withdrawal dates of the treatments. Baseline RF levels were collected before the start of each treatment to determine their potential impact on drug retention rates. Measurements of RF (IgM RF) were carried out across all participating centres using the latex agglutination nephelometric assay.

Patients were categorised into groups based on the molecular structure of the treatment they received. The groups consisted of monoclonal antibodies (mAB) (ie, IFX, ADA or GOL), fusion protein (ie, ETA) and pegylated drugs (ie, CZP).

Other baseline variables such as sex, age, diagnosis delay (the time difference between symptom onset and diagnosis), disease duration (the time difference between symptom onset and treatment initiation), presence of anti-citrullinated protein autoantibodies (ACPA), Disease Activity Score (DAS) using 28 joint counts (DAS28), concomitant treatment with methotrexate and number of previous ts/bDMARDs, were collected. For patients contributing more than one treatment to the analysis, baseline data were assessed at each initiation visit.

Statistical analysis

Descriptive data are presented as the mean and SD for continuous variables and as absolute frequencies and percentages for categorical variables.

The quartiles of the baseline RF levels were used as cut-offs to classify patients: ≥60 IU/mL (≥Q2) were classified as high and ≥200 IU/mL (≥Q3) as very high. In addition, patients were also classified as <60 IU/mL (<Q2) and <200 IU/mL (<Q3) to evaluate whether differences were found above but not below the cut-offs.

To evaluate the retention rate of the three molecular structures (CZP, mAB and ETA) in the overall population and based on baseline RF levels, we conducted the log-rank test and used Kaplan-Meier curves. In addition, Cox regressions and HRs were calculated considering the treatment with CZP as the reference. The same analysis was performed but stratifying patients into non-naïve and naïve groups (non-naïve patients had received at least one previous ts/bDMARD, while naïve patients had not received any previous ts/bDMARD). A sensitivity analysis was conducted using patients who contributed with only one treatment.

To address the potential imbalance of baseline characteristics across treatment groups, we performed a sensitivity analysis using propensity score matching. This propensity score was generated based on three key variables selected from a regression analysis to identify those associated with the outcome (age, concomitant methotrexate and previous ts/bDMARD use), and it represents the likelihood of receiving CZP, mAB or ETA treatment, conditioned on the individual baseline characteristics.[7]

Table 2 Baseline characteristics of matched populations using propensity score

	CZP N=129 Mean (SD)	mAB N=129 Mean (SD)	P value CZP vs mAB	ETA N=129 Mean (SD)	P value CZP vs ETA
Sex (female), n (%)	111 (86.0)	108 (83.7)	0.602	100 (77.5)	0.076
Age	49.1 (12.8)	49.0 (12.4)	0.929	48.9 (12.2)	0.901
Diagnosis delay (years)	0.6 (1.8)	1.6 (2.5)	0.004	1.3 (2.6)	0.067
Disease duration (years)	2.1 (4.4)	5.7 (6.8)	0.001	4.3 (7.1)	0.021
Rheumatoid factor positive, n (%)	97 (75.2)	95 (73.6)	0.775	84 (65.1)	0.077
Rheumatoid factor levels (IU/mL)	249.8 (426.6)	323.0 (1431.2)	0.578	353.0 (1506.9)	0.455
ACPA positive, n (%)	78/98 (79.6)	55/71 (77.5)	0.739	60/80 (75.0)	0.465
DAS28	4.9 (1.3)	4.7 (1.3)	0.386	5.2 (1.1)	0.084
Concomitant methotrexate, n (%)	58 (45.0%)	58 (45.0)	1.000	58 (45.0)	1.000
≥1 previous ts/bDMARD, n (%)	50 (38.8)	50 (38.8)	1.000	50 (38.8)	1.000

ACPA, anti-citrullinated protein autoantibodies ; CZP, certolizumab pegol; DAS28, Disease Activity Score 28; ETA, etanercept; mAB, monoclonal antibodies (infliximab, adalimumab and golimumab); ts/bDMARD, targeted synthetics/ biological disease-modifying antirheumatic drugs.

These three variables were significantly different across treatment groups at baseline, and they could have a potential effect on the retention rate of the drugs.

Two separate propensity score matching analyses were conducted: one to compare CZP versus mAB and another to compare CZP versus ETA. Once the CZP group and the control group (either mAB or ETA) were matched using the propensity score, they became comparable in terms of all the covariates except treatment received.[8] Subsequently, new log-rank tests, Kaplan-Meier curves and Cox regressions were conducted in the matched populations to evaluate the retention rate of CZP versus mAB and CZP versus ETA according to the baseline levels of RF.

All statistical analyses were two-sided, and a p value<0.05 was considered to indicate statistical significance. Data management and statistical analysis were conducted using RStudio V.1.4.

Handling of missing data

Patients with missing data regarding either baseline RF levels or the date of treatment initiation or withdrawal were excluded.

RESULTS

The initial population comprised 671 patients who underwent 791 treatments. After excluding 33 patients (accounting for 39 treatments) due to missing data on RF levels, the final population consisted of 638 patients and 752 treatments (with 537, 89, 11 and 1 patients participating in the analysis with one, two, three and four treatments, respectively).

The baseline characteristics of both the overall population and the different treatment groups are presented in table 1. Among the patients, 80.9% were female, and the mean age was 53.0 (±12.2). Concomitant methotrexate was used by 60% of the patients, and 29.3% had prior treatment with ts/bDMARD.

The distribution of patients across treatment groups was as follows: 132 received CZP, 439 received mAB and 181 received ETA. On comparing the treatment groups, we observed that patients receiving mAB were older, while those receiving CZP had a lower utilisation of concomitant methotrexate.

Retention rate regarding the baseline levels of rheumatoid factor in the overall population

In the overall analysis, the median retention rates for CZP, mAB and ETA were found to be similar across treatment groups (log-rank test p value=0.340) (online supplemental table 1).

When stratifying patients according to the baseline factor levels, no differences were found in the retention rate across treatments. Among patients with very high baseline RF levels (≥200 IU/mL), a trend towards a longer retention rate was observed for those receiving CZP (median 5.8 years (95% CI 2.1 to NA) compared with mAB (median 3.7 years (95% CI 2.2 to NA) and ETA (median 3.1 years (95% CI 1.2 to 6.1), although these differences were non-significant (log-rank test p value=0.180) (online supplemental table 1).

Retention rate regarding the baseline levels of rheumatoid factor and the previous use of ts/bDMARDs

Naïve patients

A total of 526 patients had not received previous ts/bDMARDs. The baseline characteristics of this subgroup are presented in online supplemental table 2. Patients in the CZP group were younger and used concomitant methotrexate less frequently than those in the mAB and ETA groups (45.6%, 65.3% and 69.2%, respectively, p=0.001).

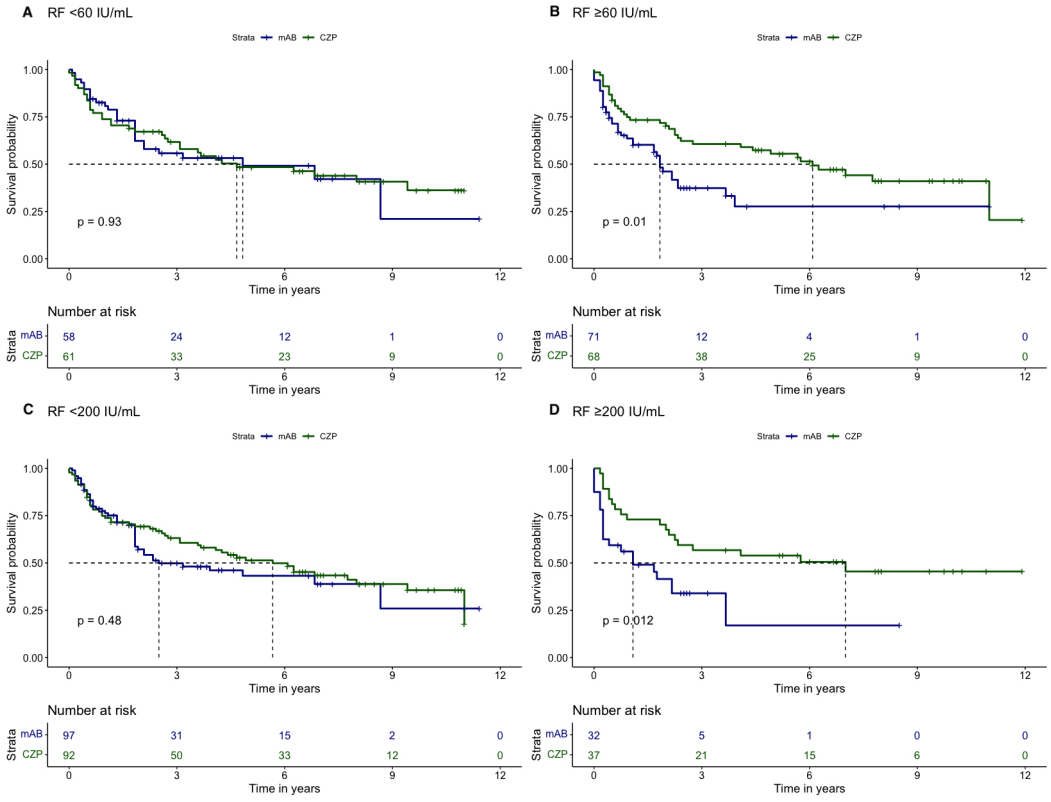

Figure 2 Comparison of the retention rate between CZP and mAB matched populations regarding the baseline levels of rheumatoid factor. Matched populations using propensity score (according to age, concomitant methotrexate and previous targeted synthetic/biological disease-modifying antirheumatic drugs). Analysis in matched populations (CZP vs mAB): (A) rheumatoid factor <60 IU/mL; (B) rheumatoid factor ≥60 IU/mL (high levels); (C) rheumatoid factor <200 IU/mL; and (D) rheumatoid factor ≥200 IU/mL (very high levels). CZP, certolizumab pegol; mAB, monoclonal antibodies (ie, adalimumab, infliximab and golimumab); RF, rheumatoid factor.

Among the naïve patients, the retention rates of CZP, mAB and ETA were found to be similar in both the high (≥60 IU/mL) and very high RF (≥200 IU/mL) groups (figure 1 and online supplemental table 3). Additionally, there were no significant differences in retention rates observed among subgroups with RF levels <60 IU/mL and RF levels <200 IU/mL (figure 1 and online supplemental table 3).

Non-naïve patients

A total of 218 patients had previously received ts/bDMARD, and their baseline characteristics are represented in online supplemental table 2. Patients from the CZP, mAB and ETA groups displayed similar baseline characteristics.

In patients with high baseline RF levels (≥60 IU/mL), the retention rate of CZP was significantly longer than that of mAB and ETA (log-rank test p value=0.016). HRs confirmed these results, with an HR of 2.6 (95% CI 1.3 to 5.4) for mAB versus CZP and HR of 2.7 (95% CI 1.2 to 5.7) for ETA versus CZP (online supplemental table 3). Similarly, in patients with very high RF levels (≥200 IU/mL), CZP demonstrated a significantly longer retention rate than mAB and ETA (log-rank test p value=0.009), with an HR of 2.6 (95% CI 0.9 to 8.0) for mAB versus CZP and an HR of 5.2 (95% CI 1.6 to 16.3) for ETA versus CZP (figure 1 and online supplemental table 3). Conversely, the retention rates of CZP, mAB and ETA were found to be similar in patients with RF levels <60 IU/mL and <200 IU/mL (figure 1 and online supplemental table 3). These results were confirmed in a sensitivity analysis including patients who contributed with only one treatment (online supplemental table 4).

Analysis after matching patients using a propensity score technique

CZP versus mAB

A sensitivity analysis using propensity score matching based on age, concomitant methotrexate and previous ts/bDMARD use was performed. The baseline characteristics of the matched population are displayed in table 2, showing well-balanced groups.

After matching populations, CZP patients exhibited a longer retention rate in comparison with mAB in patients with high (≥60 IU/mL) (HR 1.8 (95% CI 1.1 to 2.9) for mAB vs CZP) and very high RF levels (≥200 IU/mL) (HR 2.3 (95% CI 1.2 to 4.3) for mAB vs CZP). Interestingly, significant differences were not found in patients with RF<60 IU/mL (HR 1.0 (95% CI 0.6 to 1.7)) or in patients with RF<200 IU/mL (HR 1.2 (95% CI 0.8 to 1.7)) (figure 2 and table 3).

Table 3 Retention rate between CZP and mAB, and between CZP and ETA regarding the baseline levels of rheumatoid factor after matching populations using propensity score

		Treatment	N	Number of withdrawals	Median (95% CI) years*	P value log-rank test	HR (95% CI)	P value HR
Matched population: CZP vs mAB	≥60 IU/mL (high RF)	CZP	68	36 (52.9%)	6.1 (2.8 to NA)	0.010	Reference	0.011
		mAB	71	40 (56.3%)	1.8 (1.1 to 3.9)		1.8 (1.1 to 2.9)	
	≥200 IU/mL (very high RF)	CZP	37	19 (51.4%)	7.0 (2.3 to NA)	0.012	Reference	0.013
		mAB	32	21 (65.6%)	1.1 (0.3 to NA)		2.3 (1.2 to 4.3)	
	<60 IU/mL	CZP	61	34 (55.7%)	4.7 (3.1 to NA)	0.930	Reference	0.911
		mAB	58	27 (46.6%)	4.8 (2.1 to NA)		1.0 (0.6–1.7)	
	<200 IU/mL	CZP	92	51 (55.4%)	5.7 (3.6 to NA)	0.480	Reference	0.465
		mAB	97	46 (47.4%)	2.5 (1.8 to NA)		1.2 (0.8 to 1.7)	
Matched population: CZP vs ETA	≥60 IU/mL (high RF)	CZP	68	36 (52.9%)	6.1 (2.8 to NA)	<0.001	Reference	<0.001
		ETA	60	48 (80.0%)	0.9 (0.4 to 2.2)		2.2 (1.4 to 3.4)	
	≥200 IU/mL (very high RF)	CZP	37	19 (51.4%)	7.0 (2.3 to NA)	<0.001	Reference	<0.001
		ETA	27	24 (88.9%)	0.6 (0.3 to 4.3)		2.8 (1.5 to 5.2)	
	<60 IU/mL	CZP	61	34 (55.7%)	4.7 (3.1 to NA)	0.140	Reference	0.154
		ETA	69	39 (56.5%)	9.1 (8.2 to NA)		0.7 (0.4 to 1.1)	
	<200 IU/mL	CZP	92	51 (55.4%)	5.7 (3.6 to NA)	0.760	Reference	0.796
		ETA	102	54 (52.9%)	8.2 (3.4 to 10.6)		0.9 (0.6 to 1.4)	

*NA (non-available data) on the upper 95% CI limit of the median years means that the upper limit of the survival curve did not reach 50%.
CZP, certolizumab pegol; ETA, etanercept; mAB, monoclonal antibodies (infliximab, adalimumab and golimumab); NA, non-available; RF, rheumatoid factor.

CZP versus ETA

Sensitivity analysis using the propensity score was also conducted to compare CZP versus ETA. The baseline characteristics of the matched population are represented in table 3.

A significantly shorter retention rate was found for ETA than for CZP in patients with high (≥60 IU/mL) (HR 2.2 (95% CI 1.4 to 3.4)) and very high (≥200 IU/mL) (HR 2.8 (95% CI 1.5 to 5.2)) levels (figure 3 and online supplemental table 3). However, no significant differences in the retention rate between groups were found in patients with RF<60 IU/mL (HR 0.7 (95% CI 0.4 to 1.1)) and in patients with RF<200 IU/mL (HR 0.9 (95% CI 0.6 to 1.4)) (figure 3 and table 3).

DISCUSSION

In this retrospective multicentre study, we investigated the retention rate of the various TNFi groups according to the baseline RF levels. These results suggest that, among patients who have received previous ts/bDMARDs (ie, non-naïve patients), CZP demonstrated a longer retention rate among patients with high RF levels (≥60 IU/mL) in comparison to mAB and ETA and in comparison to ETA in patients very high levels (≥200 IU/mL), while these differences were not found in patients with <60 IU/mL or<200 IU/mL levels. Furthermore, a sensitivity analysis using a propensity score approach showed that patients with high and very high RF levels exhibited longer retention rates with CZP than with mAB and ETA, irrespective of age, the concomitant use of methotrexate and their treatment history (naïve or non-naïve). These findings reinforce the hypothesis of the potential role of RF in binding the Fc fragment (which is absent in CZP) and in neutralising the effect of TNFi that contains an Fc portion. Thus, these results support the suitability of the use of CZP in patients with elevated RF levels, as they seem to show a lower likelihood of treatment discontinuation.

While this study focuses on the effect of elevated RF in TNFi approved in Europe, it is important to note the existence of an additional TNFi available in Japan called ozoralizumab. This particular drug features a humanised variable domain on a heavy chain.[9] Notably, ozoralizumab lacks an Fc portion in its structure, suggesting a potential for a higher retention rate compared with other TNFi. Furthermore, we did not assess the impact of ACPA on the retention rate because ACPA specifically targets citrullinated proteins rather than IgG1, making its involvement in the IgG1-Fc clearance process unlikely.[10] Additionally, the presence of a potential confounding effect should be noted, as patients with higher ACPA levels often exhibit elevated RF levels.

RF positivity in individuals with RA has been linked to high disease activity and disease progression,[11 12] while elevated pretreatment RF levels have been associated with suboptimal clinical responses to TNFi.[13–15] The presence of the Fc region in TNFi may indeed play an important role in treatment response in patients with high RF levels. A recent post hoc

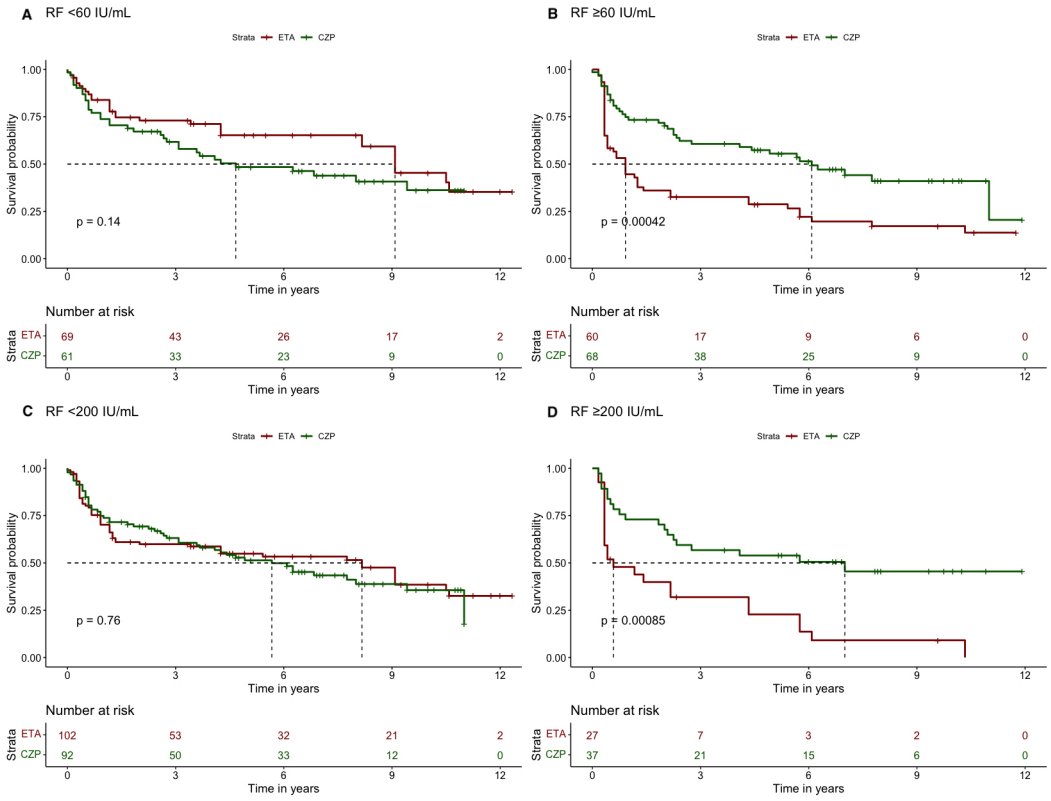

Figure 3 Comparison of the retention rate between CZP and ETA matched populations regarding the baseline levels of rheumatoid factor. Matched populations using propensity score (according to age, concomitant methotrexate and previous ts/bDMARDs). Analysis in matched populations (CZP vs ETA): (A) rheumatoid factor <60 IU/mL; (B) rheumatoid factor ≥60 IU/mL (high levels); (C) rheumatoid factor <200 IU/mL; and (D) rheumatoid factor ≥200 IU/mL (very high levels). CZP, certolizumab pegol; ETA, etanercept; RF, rheumatoid factor.

analysis incorporating data from six clinical trials involving patients with RA treated with CZP plus methotrexate versus ADA plus methotrexate, revealed that, within the highest baseline RF level quartile, there is a probability of more than 36% to achieve DAS28 low disease activity or remission in the CZP plus methotrexate compared with the ADA plus methotrexate group. This finding suggested that the impact of high baseline RF levels on CZP efficacy might not be as pronounced as that observed in ADA efficacy.[16] Similarly, a recent analysis in the phase 4 EXXELERATE trial comparing the efficacy and safety of CZP to ADA demonstrated that patients with RF>203 IU/mL (>Q3) treated with CZP had similar drug concentrations and clinical responses to patients with low levels, a pattern not observed in patients treated with ADA.[17] Interestingly, the third quartile of RF in our population is similar to that from these clinical trials, suggesting that results from the trials could be extrapolated to clinical practice. Our findings revealed a longer retention rate for CZP than for mAB and ETA within non-naïve patients with high and very high RF levels, a profile that can be considered 'severe'. Interestingly, baseline characteristics were comparable across treatment groups in these non-naïve patients, demonstrating similar percentages of women and concomitant methotrexate usage, as well as similar mean age and disease duration. It is well established that combining TNFi with methotrexate can lead to better treatment outcomes, including improved efficacy, longer retention rates and higher rates of disease remission or low disease activity.[18–20] Consequently, the resemblance of patient profiles across groups and the consistent utilisation of concomitant methotrexate further bolsters our findings, eliminating the possibility of baseline characteristic imbalances as the cause of differences in retention rates.

Among naïve patients, no significant differences were found in the retention rate in CZP-treated individuals in comparison with mAB and ETA in patients with high or very high RF levels. We have several explanations for this observed lack of significance. First, it is widely acknowledged that TNFi exhibits remarkable efficacy as a first-line treatment for patients with RA. Moreover, treatment-naïve patients tend to respond more favourably than non-naïve patients.[21] This inherent tendency poses a challenge in discerning differences among various drugs, as the likelihood of a positive response remains high regardless of RF levels. Second, it should be noted that the mAB category comprises three distinct drugs (ie, IFX, ADA and GOL), each potentially exhibiting diverse responses based on RF levels. Nonetheless, we decided to consolidate these three drugs into a single group primarily due to their similar biological structure. Furthermore, this decision also served to ensure the study's statistical power. Lastly, we observed that the naïve patients had lower levels of RF (although

non-significant) in comparison with non-naïve patients, which could influence to some extent the absence of differences in the retention rate in this population.

A sensitivity analysis was performed employing propensity score matching to enhance the precision of the results. After matching the populations by age, concomitant methotrexate and previous use of ts/bDMARDs (variables that were unbalanced across treatment groups in the original population), we confirmed the significantly longer retention rate of CZP in comparison with mAB and ETA among patients with high and very high RF levels. These findings suggest that CZP behaves better than mAB and ETA within this profile of patients, regardless of the age, of whether the drug is prescribed as a first-line or further-line treatment and regardless of the concomitant use of methotrexate. We would like to highlight these results since propensity score matching confers robustness to these findings, as it makes covariables well-balanced between groups and reduces selection bias inherent to observational studies. The reason to include age in the propensity score was that older patients may have a high prevalence of comorbidities that could lead to a premature withdrawal of the drug. In fact, comorbid conditions pose challenges in managing RA because of the contraindications for certain drugs, perpetuation of the inflammation and treatment non-adherence.[22 23] It should be clarified that, although the disease duration varied across groups, there was a collinearity between age and disease duration. Consequently, we opted to match the population based solely on age rather than on both variables. However, we acknowledge that a full balance across all baseline variables was not achieved after the propensity score matching. Furthermore, concomitant methotrexate was also included to balance treatment groups due to the effect of this drug on improving the efficacy and retention rates of TNFi (as explained above).

This study has both limitations and strengths. One limitation lies in its retrospective design, which could contribute to the presence of missing data in certain variables, such as smoking status, methotrexate dose or the use of concomitant glucocorticoids, as well as disease activity measures, precluding to evaluation of the RF levels on treatment efficacy. However, it is important to note that patients with missing data for crucial variables, such as RF levels or dates of TNFi initiation and withdrawal, were excluded. As a result, the impact of these missing data on the results has been mitigated, but we must acknowledge that this may have introduced a selection bias in our study. Additionally, there may be an inherent imbalance in patient numbers across treatment groups. Nonetheless, this distribution reflects the prescription trends observed in clinical practice. Certainly, we aimed to include only treatments prescribed after 2010, which is when all TNFi options became accessible in Spain. Another limitation is the potential effect of induction regimens, as it has been demonstrated that RF titres are associated with IFX levels and with IFX dose.[24] In our study, both the mAB (ie, specifically in IFX-treated patients) and the CZP group involve induction regimens in their posology, but the impact of this induction on the retention rate has not been assessed. One additional weakness is the absence of information regarding the specific drug prescribed before the initiation of TNFi, which prevents the conduct of subanalyses to evaluate the retention rate after tsDMARDs. The last limitation is represented by the lack of data on anti-drug antibodies, which may influence the TNFi retention rate, especially in patients in monotherapy. However, the imbalance in the prevalence of patients in monotherapy (ie, without concomitant use of methotrexate) between groups has been solved through the use of a propensity score technique. On the other hand, one of the main strengths of our study is the novelty of the topic, since very few investigations have evaluated the potential influence of RF levels on TNFi retention rates among patients with RA.[3–5 16] Furthermore, the multicentre and observational design provides a reliable picture of the utilisation patterns and persistence of TNFi treatments among patients with RA in routine clinical practice.

This study's findings are in line with previous publications in the field and could provide valuable insights for clinicians when making informed decisions about the most suitable treatment approach for their patients with RA based on individual needs and the molecular characteristics of the drugs. Particularly, these findings highlight the importance of considering RF levels and the presence of the Fc fragment when selecting the most suitable treatment approach for these patients. The observed longer retention rates associated with CZP suggest the potential for cost reduction through minimised cycling and switching across treatments. This emphasises the practical clinical relevance of our study, aiding clinicians in optimising patient with RA outcomes while managing costs-effectively.

In summary, these results suggest that the absence of the Fc fragment in CZP may contribute to a longer retention rate in patients with high and very high baseline levels of RF compared with mAB and ETA regardless of age, concomitant methotrexate and prior ts/bDMARD utilisation. These findings can potentially provide novel perspectives for the personalised management of patients with RA.

Author affiliations
[1]Rheumatology, Reina Sofia University Hospital, Cordoba, Spain
[2]GC05, Maimonides Biomedical Research Institute of Cordoba, Cordoba, Spain
[3]Medical and Surgical Sciences, University of Cordoba, Cordoba, Spain
[4]Rheumatology, La Paz University Hospital, Madrid, Spain
[5]IdiPAZ, Madrid, Spain
[6]Rheumatology, Son Llatzer University Hospital, Palma de Mallorca, Spain
[7]Rheumatology, Clinic Hospital, Barcelona, Spain
[8]Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[9]Rheumatology, University Hospital of Jaen, Jaén, Spain
[10]Rheumatology, Hospital Regional Universitario de Málaga, Málaga, Spain
[11]Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain
[12]Medicina, Univeristy of Málaga, Málaga, Spain
[13]Rheumatology, Miguel Servet University Hospital, Zaragoza, Spain

Twitter Clementina López-Medina @clemenlpez

Contributors CL-M and AE-C contributed to the study conceptualisation. JC, MCA-A, FC, CP-R, AM-F, AB, RF, AJ-M, VR-E, LS, CD-T, FJG-N, IA-O, NM-V, SM-A, MSM-G and RO-C contributed to investigation and data collection. CL-M contributed to the study by analysing data. CL-M contributed to drafting the article. All the coauthors of this manuscript have revised critically the manuscript

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ORCID iDs
Clementina López-Medina http://orcid.org/0000-0002-2309-5837
Chamaida Plasencia-Rodríguez http://orcid.org/0000-0003-3503-9047
Ana Martínez-Feito http://orcid.org/0000-0002-5580-8387
Alejandro Balsa http://orcid.org/0000-0001-8070-7062
Natalia Mena-Vázquez http://orcid.org/0000-0001-6173-2051
Sara Manrique-Arija http://orcid.org/0000-0003-2284-7846

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