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How elderly rheumatoid arthritis patients respond at one year of treatment with certolizumab pegol

Vicenç Torrente-Segarra[1] · Manuel Fernandez Prada[2] · Rosa Expósito Moliner[3] · Noemí Patricia Garrido Puñal[4] · Amalia Sánchez-Andrade Fernández[5] · José Ramón Lamua Riazuelo[6] · Alejandro Olivé[7] · Juan Víctor Tovar Beltrán[8] on behalf of RENACER Study Group (REgistro NAcional CERtolizumab)

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Dear Editor,

Several tumor necrosis factor inhibitors (TNFi) have been released in the last two decades for the treatment of rheumatoid arthritis (RA). The efficacy and safety of Certolizumab pegol (CZP), a PEGilated TNFi, is well established, as reported in randomized clinical trials (RCT) [1, 2]. Around 30% of RA patients are within the age range of 65 years or older, however, they are usually excluded from the RCTs. Elderly patients associate a declining of immune cell function and have increased risk of adverse drug reaction, infection and a higher rate of comorbidities that may influence immunosupressant treatment decisions [3–5]. Thus, scant data on both safety and effectiveness of biological disease modifying drugs (bDMARD) in clinical practice in elderly population is currently available [6]. The aim of this study was to determine the effectiveness, safety and survival of CZP in elderly-onset RA patients (EORA) in a real world setting at 12-month follow-up and compared it with young-onset RA (YORA) counterparts. We performed a prospective observational study with the following inclusion and exclusion criteria, RA patients who initiated CZP as per the discretion of the treating physician because of active RA based on Spanish Society Guidelines [7] were included and patients who could not completed follow-up visits were excluded. Socio-demographics, tender and swollen joint counts, 28-joint disease activity score (DAS28), erythrocyte sedimentation rate, C-reactive protein, health assessment

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✉ Vicenç Torrente-Segarra
vtorrente@hsjdbcn.org; vtorrente@csap.cat

Manuel Fernandez Prada
manfernandez@telefonica.net

Rosa Expósito Moliner
rosaex@euskalnet.net

Noemí Patricia Garrido Puñal
noemi.punal@gmail.com

Amalia Sánchez-Andrade Fernández
amalia.sanchez-andrade.fernandez@sergas.es

José Ramón Lamua Riazuelo
txerralamua@hotmail.com

Alejandro Olivé
aolive@germanstries.cat

Juan Víctor Tovar Beltrán
tovar_jvi@gva.es

[1] Rheumatology Department, Hospital General Hospitalet-Sant Joan Despí Moisès Broggi, C/Avinguda Josep Molins 29-41, 08906 Hospitalet Llobregat, Catalunya, Spain

[2] Rheumatology Department, Hospital Universitario de Guadalajara, Guadalajara, Spain

[3] Rheumatology Department, Hospital Comarcal Laredo, Laredo, Spain

[4] Rheumatology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain

[5] Rheumatology Department, Complejo Hospital Universitario Lucus Augusti, Lugo, Spain

[6] Rheumatology Department, Hospital Universitario de Henares, Alcalá de Henares, Spain

[7] Rheumatology Department, Hospital Germans Tries i Pujol, Badalona, Spain

[8] Rheumatology Department, Hospital General Universitario de Elche, Elche, Spain

questionnaire, previous and current use of prednisone-equivalent, conventional synthetic DMARD (csDMARD) and bDMARD were collected at baseline and 12-month assessment. Baseline rheumatoid factor and citrulline antibodies and drug-related adverse event presence and CZP discontinuation date (if applicable) were collected. Effectiveness was determined by both DAS28 remission rate and EULAR Good/Moderate Response. Descriptive, comparative analyses and Kaplan–Meier life-table method for drug survival curves were performed between '<65 years-old' (YORA) and '≥65 years-old' (EORA) patients, by Student's T, U-Mann-Whitney, Chi square and Friedman test as appropriate; Kolmogorov–Smirnov test was used to verify continuous variables distribution normalcy. A total of 501 RA patients were included: 78.6% women, mean age 53.6 years (± 13.2 SD), 23% were aged ≥ 65 year and mean disease duration 7.5 year (± 7.3 SD). Baseline features are shown in Table 1. Summarizing, we observed several baseline statistically significant differences: EORA patients showed older age and more disease duration, comorbidities, higher DAS28, HAQ, baseline ESR and CRP; YORA patients showed more csDMARD combination at CZP initiation

Table 1 Baseline features and clinical and safety outcomes comparing young and adult-onset rheumatoid arthritis patients

	Young-onset rheumatoid arthritis ($n = 382$)	Elderly-onset rheumatoid arthritis ($n = 114$)	p value
Baseline features			
Age (years)	48.4 ± 10.2	70.8 ± 4.5	< 0.001
Female gender	77.7%	92%	0.501
Disease duration (years)	6.7 ± 6.5	10.4 ± 9.1	< 0.001
Smoking status (current or ex-smoker)	33.5%	20.2%	0.024
Number of previous bDMARD	0.8 ± 1.2	0.8 ± 1.2	0.963
Bio-naive at CZP onset (yes)	44%	53%	0.582
CZP monotherapy (yes)	79.8%	75.4%	0.779
Prednisone use (yes)	67%	68.4%	0.779
Prednisone-equivalent dosage (mg/d)	8.1 ± 6.6	7.4 ± 4.5	0.975
28-Joint tender joint count	9.1 ± 6.2	9.9 ± 6,4	0.264
28-Joint swollen joint count	6.5 ± 5.0	7.4 ± 5.4	0.137
DAS28	4.6 ± 1.1	5.0 ± 1.0	< 0.001
Erythrocyte sedimentation rate (value)	26.9 ± 22.0	36.6 ± 25.3	< 0.001
C-reactive protein (mg/L)	5.6 ± 10.0	11.6 ± 27.2	0.021
Health assessment questionnaire	1.2 ± 0.7	1.4 ± 0.6	0.028
Rheumatoid factor (positive)	53.8%	55.3%	0.787
Anti-citruline protein antibodies (positive)	68%	74.6%	0.565
Comorbidities (≥ 1 of the following condition: pulmonary, cardiovascular, diabetes mellitus, high blood pressure, malignancy, gastrointestinal, osteoporosis, thyroidal, dyslipidaemia, depression)	34.8%	46.5%	0.024
Clinical and safety outcomes at the end of follow-up			
28-Joint tender joint count	3.6 ± 5.1	3.4 ± 4.3	0.714
28-Joint swollen joint count	2.1 ± 3.3	2.1 ± 3.3	0.479
Disease activity score-28	3.1 ± 1.3	3.4 ± 1.2	0.03
Disease activity score-28 remission	43.0%	31.3%	0.026
Health assessment questionnaire	0.9 ± 0.7	1.1 ± 0.7	0.063
Low disease activity (DAS28)	57.5%	47.3%	0.057
Good/moderate EULAR response	67.7%	75.0%	0.145
Prednisone use	42.7%	61.4%	< 0.001
Prednisone-equivalent dosage (mg/d)	4.1 ± 4.9	5.4 ± 4.6	0.005
Safety			
Drug-related adverse events	11.3%	19.3%	0.026
Survival			
Discontinuation	25.4%	32.5%	0.133

bDMARD biological disease modifying drugs, *CZP* certolizumab PEGol, *DAS28* 28-joint Disease Activity Score, *EULAR* European League Against Rheumatism, *mg/d* daily milligrams, *mg/L* milligrams per liter

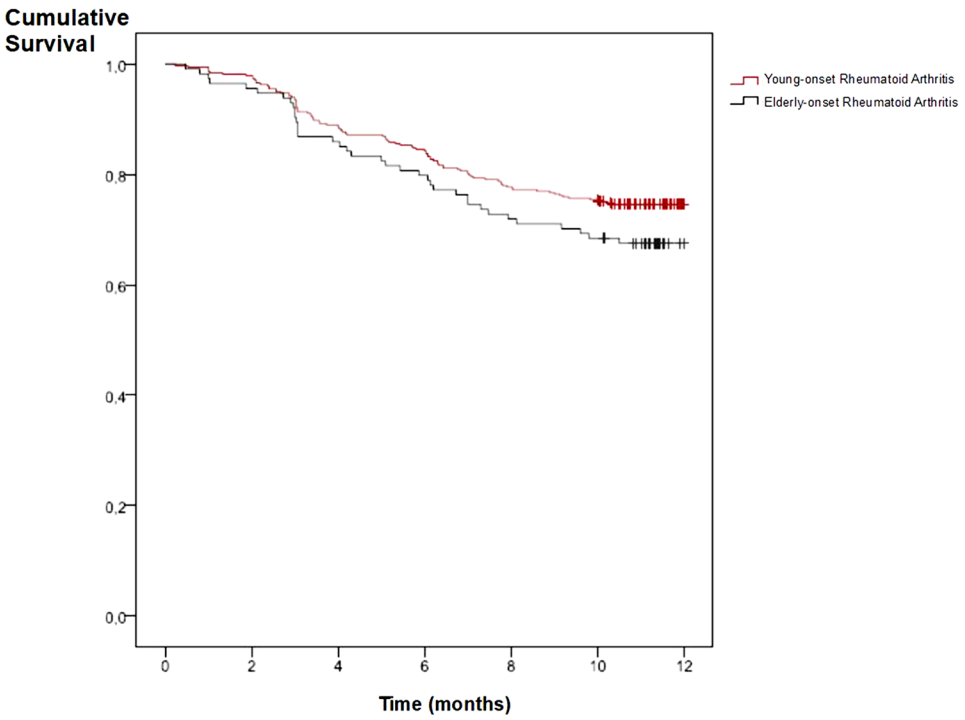

Fig. 1 Survival rate for Certolizumab PEGol comparing young and adult-onset rheumatoid arthritis patients ($p = 0.133$)

and higher percentage of smokers. At the end of follow-up, EORA patients showed higher DAS28 score, prednisone-equivalent use and dosage and adverse events, while YORA patients showed higher DAS28 remission rate than EORA. All assessed variables are shown in Table 1. Survival of CZP was not statistically different (Fig. 1). Therefore, the effectiveness on CZP-treated patients was similar, irrespective of the age. Only when applying DAS28 Remission criteria, EORA patients showed worse outcome. Thus, adverse events led to CZP discontinuation in a higher number of EORA patients when compared to YORA, although no major adverse effects were seen (Supplementary Material). However, after 1 year of real-life data in CZP users, EORA patients showed positive results. Nevertheless, we found a higher number of EORA patients that still were receiving prednisone and at a higher dosage after 1 year of CZP initiation, compared to YORA. Data available in EORA are scant, which is a usually forgotten population in RCT while very constantly present in our everyday clinics. Only a few studies assessing individual bDMARD or several bDMARD at the same time, mostly TNF-inhibitors, have been performed in EORA patients. These authors have been raised particularities in EORA when compared to YORA. EORA patients tend to suffer higher frequency of bDMARD-related adverse events, including infections, which we also observed. The presence of comorbidities, higher use of prednisone and clinical variables of severity have been pointed out as potential contributors to the presence of adverse events. Nevertheless, clinical outcomes might be comparable to YORA population in terms of drug survival. At the end of first-year CZP observational period we did not find statistical differences between EORA and YORA in terms of drug survival, neither other author did with other studied TNFi [3, 8]. As limitations, we remark that EORA showed several different baseline characteristics compared to YORA. Despite CZP showed benefit within EORA patients, higher adverse event rate and discontinuations were observed compared to YORA. However, drug survival was not different. Further studies are needed to confirm our results.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study has been approved by the relevant local ethics committee (*Internal Code 13/34*) of the Hospital General Hospitalet-Moisès Broggi (Hospitalet Llobregat, Spain).

Informed consent Informed consent was obtained from all individual participants included in the study.

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