

**Safety and effectiveness in switching from reference to biosimilar rituximab in rheumatoid arthritis patients: real world experience from a single Italian rheumatology centre**

Sirs,

Over the last two decades, biological treatments have changed clinical perspectives of rheumatoid arthritis (RA) patients with the chance to achieve a condition close to healing (1-3). Ensuring the availability of innovative therapies for all patients with economic sustainability represents a major challenge for healthcare systems. Rituximab (RTX) is a chimeric monoclonal antibody against CD20 receptor approved for RA treatment and CT-P10 (CELLTRION, Inc., Incheon, Republic of Korea) is its biosimilar. As required from regulatory agencies (4), randomised controlled trials (RCTs) have shown the bioequivalence of reference and biosimilar RTX in terms of efficacy, safety and immunogenicity (5). However, no real-world data on switching from reference to biosimilar RTX in RA patients are currently available. We evaluated the safety and effectiveness of reference/biosimilar RTX switching in RA patients in real life setting.

RA patients, fulfilling the 2010 ACR/EULAR classification criteria, treated in our centre for at least 12 months with approved dosages of RTX originator (Mabthera®) were consecutive asked to switch to RTX biosimilar CT-P10 (Truxima®), after written informed consent.

Disease Activity Score 28-joint count (DAS28) and Clinical Disease Activity Index (CDAI) were evaluated before the first CT-P10 administration, and then every 12 weeks recording any adverse event (AE) or hospitalisation. The Statistical System Prism (GraphPad InStat, v. 6.0 GraphPad Software, San Diego, CA, USA) was used for statistical analysis, and *p*-value <0.05 was considered statistically significant.

Globally a case series of 62 RA patients (57 females, 91.9%) consented to switch to biosimilar RTX after a median (IQR) of 72 (36–84) months of treatment with 12 (6–14) cycles of reference RTX.

The clinical and demographic characteristics of the enrolled patients are reported in Table I. At the last follow-up visit of reference RTX, DAS28 was 2.2±1.0 and CDAI was 3.7±4.3, and no statistically significant changes in DAS28 and CDAI after switching were observed. At 52-weeks follow-up, 37/62 (59.7%) and 31/62 (50%) patients were on remission, 13/62 (21%) and 23/62 (37.1%) patients were on low-disease activity, respectively (*p*>0.05), according to DAS28 or CDAI definitions.

Considering safety, we observed 2 cases of

**Table I.** Demographic and clinical characteristics of RA cohort before RTX switching.

Female, n. (%)	57 (91.9%)		
Age, years (mean ± SD)	39.5 ± 12.2		
Disease duration, years (mean ± SD)	18.6 ± 10.2		
Erosive disease, n. (%)	38 (61.3%)		
Concomitant csDMARDs at switch, n. (%)	50 (80.6%)		
Autoimmune serology, n (%)			
RF+	24 (38.7%)		
ACPA+	36 (58.1%)		
RF+ ACPA+	19 (30.6%)		
RF- ACPA-	21 (33.9%)		
Treatment biologic line, n. (%)			
1st line*	10 (16.2%)		
2nd line	20 (32.3%)		
≥3rd line	22 (35.5%)		
	Baseline <sup>#</sup>	24 weeks	52 weeks
DAS28-CRP, median (IQR)	2.2 ( 1.4–2.7)	2.3 (1.6–2.9)	2.4 (1.7–3.1)
CDAI, median (IQR)	2.5 (1–6)	3.2 (0.9–7.5)	3.2 (1–5.7)
Event rates**	CT-P10	Originator RTX	
Major infections	1.3	2.2	
Minor infections.	5.7	6.8	
Leukopenia	0.4	0.6	
Hospitalisations	0.7	1.8	

\*Contraindications to other biologic therapies (*i.e.* concomitant lymphoma, MGUS or had Sjögren's disease secondary to RA); \*\*Event rates are number of observed events per 100 person-years, calculated by dividing the number of events by (subjects exposed x n. RTX cycles x 100 person-years); # before the first CT-P10 administration.

ACPA: anti citrullinated peptides antibody; CDAI: clinical disease activity index; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-CRP: 28 joints using C-reactive protein disease activity score; IQR: interquartile range; RF: rheumatoid factor; SD: standard deviation.

lymphopenia and one neutropenia, solved spontaneously after a transient RTX suspension. Nine patients experienced bronchial infection, and 5 were hospitalised. All cases solved after RTX suspension and antibiotic treatment. These AEs in biosimilar RTX switchers occurred after a global exposure to 11 (4–13) cycles. Similarly, 3 cases of leukopenia, 15 cases of infections with 3 hospitalisations have been already observed during reference RTX treatment, after 8 (5–12) cycles (Table I).

The efficacy and safety of CT-P10 RTX in RA patients have been evaluated by Yoo *et al.* in a phase III RCT, demonstrating its bioequivalence to reference RTX in RA patients (6). Pharmacokinetic, pharmacodynamic, immunogenicity and safety findings were comparable up to week 48, providing evidence for CT-P10 approval for RA in clinical practice.

Lacking data in real-life setting regarding the switching from reference to biosimilar RTX raised physicians' concerns on this strategy. In our real-life monocentric study, we observed that CT-P10 is an effective and well-tolerated treatment for RA patients, able to maintain good disease control after 52 weeks switching from reference RTX. The practice of switching patients in good disease control from reference drug to a biosimilar (non-medical switch) represents a clinical challenge for physicians with the perspective of financial savings for payers, and our study give evidence of efficacy and above all safety of this practice with RTX. Some limitations of our study, such as the relatively low number of enrolled patients and the absence of control group of patients continu-

ously treated with reference RTX, have to be considered. Nevertheless, we have shown no raise in infections despite of the accrual of biosimilar over reference RTX.

*Ethical approval*

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study. As part of the BIOlogical aPULian REgistry (BIOPURE), this study was approved by the Ethics Review Board of Policlinico of Bari, comitatoetico@policlinico.ba.it, protocol number 5277.

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# Letters to the Editors

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