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Clinical Outcomes in Rheumatoid Arthritis due to Tocilizumab Stock-out during COVID-19 Epidemics: A Short Case Series Report

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Abstract This short case-series reports a 6-month follow up of 5 rheumatoid arthritis patients (2 males, 3 females) 60 years-old or above, with Tocilizumab treatment which was discontinued due to stock off in July 2021. Patients switched treatment to other DMARD (Upadacitinib, Baricitinib, or Certolizumab pegol). We report clinical data and the Disease Activity Score for Rheumatoid Arthritis. Upadacitinib, Baricitinib, and Certolizumab appear therapeutically equivalent to Tocilizumab in a 6-month follow-up.

Keywords: *Tocilizumab, rheumatoid arthritis*

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1. Introduction

Tocilizumab (TZB), a recombinant humanized monoclonal antibody against the interleukin-6 receptor, is a widely used disease-modifying antirheumatic drug (DMARD) in rheumatoid arthritis (RA) [1]. In Portugal, TZB is the only available DMARD that blocks interleukin-6 receptor.

Following evidence that TZB improved mortality outcomes in hospitalized patients with Coronavirus disease 2019 (COVID-19), as levels of interleukin-6 correlate with COVID-19 severity and acute respiratory distress syndrome, TZB was used as a COVID-19 therapy [2]. Although the role of TZB for hospitalized but non-critically ill patients with COVID-19 remains unclear, its novel use led to a national stock-out which prompted rheumatologists to substitute TZB with other DMARD when caring for RA patients.

This short case series describes the clinical outcomes of seven RA patients, aged 60 years or older, during a six-month period, after their therapy was switched from TZB to other DMARD.

2. Cases Presentation

We followed all 5 RA patients (2 males, 3 females) 60 years-old or above, undergoing treatment at the Rheumatology consultation in the Faro unit of the Centro Hospitalar Universitário do Algarve, in Portugal. All patients had an active diagnosis of RA, with TZB treatment discontinued due to stock off in July 2021. Follow-up was six months for all patients and data were collected at the time of the last TZB administration (T0), one month after switching to other DMARD (T1), three months after use of the new drug (T3) and after six months under the new drug (T6). We collected data on time since the diagnosis of RA, TZB therapeutics duration, number of tender (TJ) or swollen joints (SJ), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and dosage of prednisolone used as coadjutant therapy to TZB. Following clinical guidelines [3], AR activity was also described through the use of the Disease Activity Score for Rheumatoid Arthritis (DAS28), computed with both data from ESR (DAS28 ESR) and from CRP (DAS28 CRP), in order to increase specificity for detecting AR exacerbation during the follow-up. DAS28, which results in a score between 0 and 10 indicating the activity rate of RA at that particular moment, was categorized, as proposed by the authors of the scale [4], as following: high disease activity >5.1; low disease activity ≤3.2; remission ≤2.6.

All patients gave their informed consent for this study, which was previously approved by the Ethics Committee of the *Centro Hospitalar Universitário do Algarve*. All privacy and anonymity rules and regulations for this type of study were strictly followed.

Table 1. Age and therapy for all patients (n=5)

Patient	Age (years)	Years with RA until TZB therapy	Years on TZB therapy	New therapy
P_1	66	10.5	1,09	Upadacitinib
P_2	64	9.8	3.75	Upadacitinib
P_3	72	13.7	2.87	Baricitinib
P_4	68	24.7	3.7	Certolizumab pegol
P_5	72	5.6	2.53	Baricitinib
M±SD:	68.4±3.58	12.9±7.24	2.8±1.09	

RA – rheumatoid arthritis; TZB – Tocilizumab; M – mean; SD – standard deviation.

Table 2. Rheumatoid arthritis activity during the 6-month follow-up after change in therapy (n=5)

Variables	Follow-up moments				p-value (Friedman's test)
	T_0	T_1	T_3	T_6	
Tender joints (M±DP)	1.6±1.52	1.3±1.89	0.3±0.5	1.8±1.71	0.257
Swollen joints (M±DP)	1.0±1.73	1.3±1.89	0.3±0.5	1.3±1.89	0.733
ESR (mm/h) (M±DP)	5.4±5.94	5.3±5.77	28.3±14.29	15.5±13.08	0.157
CRP (mg/dl) (M±DP)	3.0±0.0	3.0±0.0	54.1±87.49	61.2±114.36	0.207
Prednisolone (mg) (M±DP)	3.0±2.74	3.0±2.74	2.0±2.74	2.0±2.74	0.392
DAS28 SS (M±DP)	1.8±0.77	2.0±1.05	2.8±0.31	2.5±1.36	0.203
DAS28 CRP (M±DP)	2.2±0.62	2.6±1.25	2.5±0.76	2.5±0.87	0.818

ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; DAS28 – *Disease activity score using 28 joints*; M – mean; SD – standard deviation.

3. Results

Patients' age ranged between 64 and 72 years old (mean of 68.4±3.58 years). Table 1 presents RA duration, time on TZB therapy, and the new drug prescribed after TZB stock-out.

During follow-up, we recorded an increase in ESR and CPR in 2 of the 5 patients but, on the overall, these changes were statistically non-significant (Friedman's test; $p>0.05$). These two patients changed their disease activity category between T0 and T6, from remission (DAS28≤2.6) to low disease activity (DS28≤3.2), when computing DAS28 with both ESR and CRP. Table 2 shows RA activity during the 6-month follow-up after change in therapy.

4. Discussion

Our results show no benefit or prejudice of switching from TZB to another DMARD. Patient data suggest a previous adequate response to TZB and the switch in therapy, even when switching to a drug with a different mechanism of action, did not significantly impacted clinical outcomes.

The literature suggests that Baricitinib and Upadacitinib, Janus kinases inhibitors, can be a therapeutic option for RA in adults resistant to initial biologic DMARD therapy, with a similar relative safety to that of biologic DMARD, including increased risk of infections and liver function test abnormalities [5]. Their clinical use must be monitored, as there are concerns regarding possible neutropenia, hyperlipidemia, and increased serum creatinine. One advantage of these pharmacological agents is that they are orally administered. The literature suggests that adverse events may be more common with upadacitinib than with TZB [6], but none were reported by our patients.

Certolizumab pegol is administered by subcutaneous injection and neutralizes membrane-associated and soluble tumor necrosis factor (TNF)-alpha. It is the first anti-TNF for potential use in women with chronic rheumatic disease during both pregnancy [7] and breastfeeding [8].

5. Conclusion

In the set of cases followed for this study, upadacitinib, baricitinib, and certolizumab pegol appear therapeutically equivalent to TZB in a 6-month follow-up.

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Conflict of Interest

The authors declare that there are no conflicts of interest associated with this work.

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