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Effects of the Tocilizumab on Lipid Profile in Rheumatoid Arthritis

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Abstract **Original Research Article**

Introduction: Tocilizumab (TCZ) is now one of the main biomedicines in rheumatoid arthritis (RA).The disturbance of the lipid profile is very frequent during its use.The objective of this work is to determine the changes in the lipid profile in RA patients treated with tocilizumab. ***Patients and methods:*** This is a cross sectional study including patients with rheumatoid arthritis treated with tocilizumab. The study was carried out in rheumatology department in the university hospital Hassan II of Fez. Total cholesterol, triglycerides, HDL and LDL were measured in the plasma preceding TCZ and after 12 weeks of treatment. ***Results:*** Our study showed Increases in the fasting plasma lipid levels (within the normal range) from baseline and at week 12 as follows: Total cholesterol for 37, 5% of patients, LDL cholesterol for 25%, Triglycerides (TG) for 18.7% and HDL for 6.3% of patients. The statistical analysis of the different lipid parameters did not objectify significant association at baseline and at three months of treatment except for the Triglycerides (p = 0.002). ***Conclusion:*** The tocilizumab is responsible of disturbance in the lipid profile of patients with rheumatoid arthritis, but these results require confirmation on a larger number of patients, and to continue this lipid profile monitoring on a longer term.

Keywords: Rheumatoid arthritis; lipid profile; tocilizumab; triglycerides; atherogenic index.

INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic autoimmune-mediated inflammatory joint disorder, affecting 0.5-1% of the world population [1]. While RA primarily involves the synovial membrane, it has been associated with a significantly increased risk of cardiovascular disease (CVD) [2]. Compared to the general population, evidence indicates increased mortality ratio in RA and is largely due to cardiovascular disease (CVD) [3, 4]. The CVD in RA are associated to multiple of risk factors: family history of CVD, smoking, obesity, type 2 diabetes mellitus, dyslipidemia, disease associated inflammation and systemic medication, disease activity and physical inactivity due to joint destruction) [5].

Tocilizumab (TCZ) is a humanized anti-human interleukin (IL)-6 receptor blocking monoclonal antibody that recognizes both the membrane-bound and the soluble forms of IL-6 receptor. TCZ, both in combinations with methotrexate and in monotherapy, has been proven to be beneficial in decreasing disease activity, preventing structural damage and improving function in rheumatoid arthritis (RA) patients [6]. Although in early phase clinical trials, elevations in LDL cholesterol, HDL, and triglyceride levels were reported in 20–30% of RA patients treated with TCZ [7].

In the present study, we investigated the changes in the lipid metabolism of patients with rheumatoid arthritis (RA) treated with tocilizumab.

PATIENTS AND METHODS

Sixteen RA patients were included in this cross sectional study in the Rheumatology department in HASSAN II university Hospital. All patients fulfilled the 1987 criteria of the American College of Rheumatology (ACR) for RA [8]. All The patients were refractory to disease-modifying anti-rheumatic drugs (DMARDs); and received 8 mg/kg body weight of tocilizumab intravenously every 4 weeks. The following data were collected from patient registers: demographic data (age, gender), clinical history, RA disease duration in years (from the time of diagnosis), rheumatoid factor, anticycliccitrullinated peptide antibodies (ACPA).

Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein

cholesterol (LDL) and triglycerides (TG) as well as the atherogenic index was assessed at baseline and at three months of treatment.

The data were coded and analyzed using the SPSS statistical module. The mean demographic differences were examined using chi tests for dichotomous variables and independent student's t-test for continuous data. Results were considered significant if the P-value was<0.05.

RESULTS

In our study, we included sixteen patients treated for rheumatoid arthritis with tocilizumab. All the patients were women. The average age of our patients was 50 +/- 8.5 (32-64) years.12.5% of patients had diabetes and 18.8% were hypertensive. The mean of BMI was 27.2 +/- 4.4kg / m² with an obesity rate of 37.5%.One patient was known having dyslipidemia and was taking statins, and one patient had a history of myocardial infraction.81.3% of patients were Rheumatoid factor positive, and 31.3% were ACPA positive. The mean disease duration was 10+/-4, 9 years (See Table-1).

A moderate increases in the mean levels of nonfasting total cholesterol, high-density lipoprotein cholesterol, and triglycerides were seen in the third month of treatment by Tocilizumab. But no acute cardiovascular events were recorded during the study.

Total cholesterol increased in 37.5% of patients, LDL cholesterol in 25%, Triglycerides in 18.7% and HDL in 6.3% of patients.

Statistical analysis of the different lipid parameters objectified significant association at baseline and at three months of treatment only for the Triglycerides (p = 0.002) (see Table-2).

The atherogenic index calculated by CT /HDLc slightly increased for 43.7% of patients (p= 0, 7).

Table 1: Baseline demographic data of rheumatoid arthritis patients

	Patients (n = 16)
Female [n (%)]	100
Age (years)	50 +/- 8.5 (32-64)
BMI (mg/cm2)	27.2 +/- 4.4kg / m²
Comorbidity	
Hypertension [n (%)]	18.8
Diabetes [n (%)]	12.5
Dyslipidemia [n (%)]	6,25
Current smoker [n (%)]	0
RA related data	
ESR (mm/h)	32,36 ± 26,47 [8-110]
CRP (mg/dl)	21 [3-213]
Disease duration, years	10+/-4, 9
DAS28-ESR	5,74 ± 1,21 [3.9- 7.6]
DAS28- CRP	5,54 ± 1,24 [3.83 – 7.74]
Rheumatoid factor UI/ML	150 [12-1000]
ACPA UI/ML	68 [5-1000]

Table-2: The lipid profile of RA patients

	S0	**S12**	**P**
TC	1,8	2	0.115
HDL	0,51	0,58	0,385
LDL	1,09	1,17	0,514
TG	0,95	1,28	0.002
CT /HDLc	3 ,44	3,63	0,7

DISCUSSION

The Hyperlipidemia has been reported to be one of the most common adverse effects of tocilizumab. However, the underlying mechanisms remain unknown [9, 10].

The changes in lipid profiles found in RA patients included in our study are in agreement with the current knowledge in this area. Increases in total cholesterol, as well as in HDL and LDL cholesterol, have been known to occur 4–8 week after initiation of TCZ in RA patients [11].

A study of Nishimoto *et al.*, [12] with a large number of patients (164 patients) confirm the results of our study: increases in total cholesterol (29%), triglycerides (35%), and also HDL-C (24%),as well as the study of the Samurai [13]: increases in total cholesterol, triglycerides and LDL-C respectively in 38%, 17% and 26% of patients treated with Tocilizumab.

Our results showed that the atherogenic index was slightly increased for 43.7%.This result was in accordance to Smolen *et al.*, study [14], that found an

increase in the total cholesterol / HDL-C ratio in 17% of patients treated with tocilizumab. However the samurai's study [13] did not found any changes of the atherogenic index.

In this study there was no significant association at baseline and following three months of treatment except for the Triglyceride (p = 0.002). This is not consistent with the results of Delarche *et al*., [15] that showed no difference for any parameter of the lipid profile at baseline and at three months of treatment.

CONCLUSION

The tocilizumab may be responsible of disturbance of the lipid profile from controlled randomized trials, which may exacerbate the presence of pre-existing cardiovascular factors.

This study showed that the tocilizumab is responsible for a significant increase in the triglyceride and non-significant increase for the other lipid parameters. These results, although preliminary, require confirmation on a larger number of patients, and continuation of lipid profile monitoring in a longer term.

Conflict of interest: No conflict of interest was declared by the authors.

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