Cardiovascular events and change in cholesterol levels in patients with rheumatoid arthritis treated with tocilizumab: data from the REGATE Registry

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Abstract

Objective

Rheumatoid arthritis (RA) is responsible for excess mortality mainly due to cardiovascular disease. Studies have found elevated cholesterol levels in RA patients who received tocilizumab (TCZ). We studied the occurrence of major cardiovascular events in RA patients who received TCZ in current practice. We also analysed cholesterol level changes in these patients.

Methods

Data were collected from the French REGATE Registry, a multicentre observational study including patients with RA treated with TCZ. All cardiovascular complications were analysed. Changes in cholesterol levels were studied. Factors associated with major adverse cardiac and cerebrovascular events were analysed by multivariate analysis, estimating odds ratios and 95% confidence intervals.

Results

During an exposure time of 5591 patient-years (PYs), 35 cardiovascular events occurred in 33 patients, corresponding to an incidence of 0.63/100 PYs. The incidence of ischaemic stroke and cardiac ischaemia was 0.41 and 0.21/100 PYs. Age and personal history of cardiovascular events were identified as risk factors associated with cardiovascular events: OR=1.06 [95% CI 1.02-1.09] and 4.10 [1.90–8.83]. Female sex was a protective factor (OR=0.29 [95% CI 0.14–0.64]). Glucocorticoids may play a role but was not statistically significant. All cholesterol variables were increased in level after the third month of treatment with TCZ, with a 15.4%, 18.9% and 13.4% increase for total cholesterol, LDL-C and HDL-C, at 3 months.

Conclusion

In current practice, cardiovascular events occurring under TCZ treatment is in the range of what is expected in RA patients despite a global increase in cholesterol levels.

Key words

rheumatoid arthritis, tocilizumab, cardiovascular events, cholesterol

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Introduction

Patients with rheumatoid arthritis (RA) have lower life expectancy than the general population. Mortality rates for RA patients are at least twice as high as for the general population, mainly because of increased cardiovascular morbidity and mortality. This excessive cardiovascular risk is due to traditional cardiovascular risk factors and also RA severity and systemic inflammation (1-3).

During the last decades, the availability of new highly effective drugs and implementation of more intensive treatment strategies have changed the management of RA. Today, remission is the objective of the therapeutic strategy (4, 5). Recently, some authors have suggested a decrease in observed excess mortality, which may be explained by reduced systemic inflammation with better control of disease activity, leading to a decrease in cardiovascular disease.

Tocilizumab (TCZ), an interleukin-6 receptor antagonist, is a biologic agent that obtained marketing authorisation for RA with moderate to high disease activity despite treatment with synthetic disease-modifying anti-rheumatic drugs (DMARDs). Several studies, particularly clinical trials and long-term extension studies (6-10), noted elevated serum cholesterol levels among RA patients receiving TCZ with no increase in cardiovascular morbidity and mortality (11). However, no study has evaluated cardiovascular complications in a large number of RA patients receiving TCZ in current practice.

In this study, we evaluated the occurrence of major cardiovascular events and change in cholesterol levels in RA patients receiving TCZ and included in the REGistry-RoAcTEmra (REGATE) registry in France.

Material and methods

REGATE registry

The REGATE registry is a French observational multi-centre study investigating the efficacy and safety of TCZ in clinical practice in patients with active RA despite treatment with synthetic or biologic DMARDs. Patients were included from January 2011 to May 2013 in 78 centres and followed up for 5 years. Patients who had participated in pivotal studies were not included in this registry. Data were collected at baseline and then every 6 months, by using an electronic case report form. All side effects were also collected even if TCZ was stopped during follow-up. The REGATE study was conducted in full concordance with the principles of the Declaration of Helsinki and with the laws and regulations of France. This study was approved by the French authorities (Comité Consultatif sur le Traitement de l'information en matière de Recherche dans le domaine de la Santé and Commission Nationale de L'Informatique et des Libertés) and registered as no. 910346.

Objectives

The main objective was to study, in current practice, the occurrence of major cardiovascular events in RA patients receiving TCZ in the REGATE registry. We also analysed changes in levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) in this population.

Patient selection

For the first objective concerning cardiovascular safety of TCZ, RA patients were included if they had received at least one TCZ infusion and had a cardiovascular side effect termed as a major adverse cardiac and cerebrovascular event (MACCE). MACCEs were defined as ischaemic stroke, cardiac ischaemia (angina, myocardial infarction, and acute coronary syndrome), heart failure, or cardiovascular death. All events were assessed by two different investigators (MR and JM) and were analysed even if patients had stopped TCZ at the time of the adverse event.

All RA patients included in the REGATE registry and who received at least one TCZ infusion were included in the analysis of changes in cholesterol levels. TC, LDL-C and HDL-C levels were collected at baseline, at 3- and 6-month visits and at 1 year.

Statistical analysis

The incidence of major cardiovascular events is presented as events per 100 patient-years (PYs). We investigated

the association between MACCEs occurring during follow-up in REGATE registry and potential predictors such as age, sex, cardiovascular risk factors, disease severity (baseline Disease Activity Score in 28 joints [DAS28], disease duration and biological inflammation), positivity for rheumatoid factor (RF) and for anti-citrullinated peptide antibodies (ACPA), concomitant use of glucocorticoids (GCs) and current treatment with DMARDs. We used both univariate and multivariate analyses to identify risk factors of MACCEs in RA patients. Variables associated with MACCE at $p<0.20$ on univariate analysis were candidates for the multivariate model. Results of multivariate analysis are expressed as adjusted odd ratios (ORs) with 95% confidence intervals (95% CIs). $p<0.05$ was considered statistically significant.

In studying cholesterol level changes in RA patients receiving TCZ, results are expressed as mean (SD), median (range) with minimum and maximum values, and percentage change. We also analysed the change in an atherogenic index in common practice, defined as the TC/HDL-C ratio, which seems to be one of the most important predictors of cardiovascular events.

Results

Cardiovascular safety

- Characteristics of MACCE

A total of 1496 RA patients were included in the REGATE registry from 2011 to 2013. Analysis was performed on 1491 patients because 5 patients had no follow-up without any explanation. All patients received TCZ by infusion only. The mean follow-up was 3.75 years, corresponding to 5591 PYs.

During follow-up, 35 MACCEs were reported in 33 patients (2 patients had 2 cardiovascular events) corresponding to an incidence of MACCEs of 0.63/100 PYs (Table I). In total, 23 of these 35 events were ischaemic strokes (0.41/100 PYs), with 6 transient ischaemic attacks. The remaining 12 MACCEs were cardiac ischaemia (0.21/100 PYs). No heart failure or cardiovascular death was described. The mean time from TCZ initiation to the MACCE was 2.3 (SD 1.3) years. The median time from the last infusion of TCZ to the MACCE was 73 (range 0–43) days. At the time of MACCE occurrence, 48.6% of patients (17/35) were still receiving TCZ and 58.8% were in monotherapy (10/17), 35.3% combined with methotrexate (6/17), and 5.9% with leflunomide (1/17). Overall, 65.6% of patients were taking steroids at the time of the MACCE, with a mean dose of 7.5 (SD 4.9) mg/day. Most patients had moderate activity disease, with mean DAS28-erythrocyte sedimentation rate of 3.4 (SD 1.3).

Table I. Characteristics of major adverse cardiac and cerebrovascular events (MACCEs n=35) in patients (n=33).

Type of MACCE (%)	
Ischaemic stroke	65.7 (23/35)
Cardiac ischaemia	34.3 (12/35)
Incidence of MACCEs (/100 PY)	0.63
Incidence of ischaemic strokes	0.41
Incidence of cardiac ischaemia	0.21
Time since TCZ initiation and MACCE (years)	
Mean (SD)	2.3 (1.3)
Median (min-max)	2.4 (0-4.7)
Time since last infusion of TCZ and MACCE (years)	
Mean (SD)	1.1 (1.4)
Median (min-max)	0.2 (0-4.3)
Treatment with TCZ during MACCE, n (% of events)	17 (48.6)
TCZ monotherapy	10 (58.8)
TCZ+MTX	6 (35.3)
TCZ+LFN	1 (5.9)
Dose of TCZ (% of patients)	
4 mg/kg	10
8 mg/kg	90
Treatment of patients not still receiving TCZ during MACCE, n	7: other DMARDb (3 abatacept, 2 rituximab, 1 etanercept, 1 infliximab) 11: no DMARDb
GCs during MACCE (% of patients)	65.6
Available data, n (%)	32/35 (91.4)
Dose of GCs during MACCE (mg/day)	
Available data, n (%)	21 (100)
Mean (SD)	7.5 (4.9)
Median (min-max)	6.0 (1.0-20.0)
CRP level (mg/L) during MACCE	
Available data, n (%)	17 (48.6)
Mean (SD)	5.2 (5.7)
Median (min-max)	2.5 (0.1-19)
DAS28-ESR during MACCE	
Available data, n (%)	16 (45.7)
Mean (SD)	3.4 (1.3)
Median (min-max)	3.1 (1.4-5.9)
DAS28-CRP during MACCE	
Available data, n (%)	14 (40.0)
Mean (SD)	3.6 (1.2)
Median (min-max)	3.3 (1.9-5.8)

MACCE: major adverse cardiac and cerebrovascular event; PY: patient-years; TCZ: tocilizumab; MTX: methotrexate; LFN: leflunomide; GC: glucocorticoids; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Only one patient had definitely stopped TCZ after the MACCE. There was only one temporary stop. For other patients, TCZ administration was as before the MACCE occurrence.

- Risk factors of MACCE

On univariate analysis of RA patients with and without MACCE during follow-up, factors associated with a MACCE were age ($p<10^{-3}$), female sex ($p<10^{-3}$), personal history of cardiovascular disease ($p<10^{-3}$), arterial hypertension ($p=0.048$), hypercholesterolae-

Table II. Risk factors of MACCEs: univariate and multivariate analysis.

Characteristics at baseline	Univariate analysis			Multivariate analysis	
	Patients with MACCE (n=33)	Patients without MACCE (n=1468)	*p*-value	OR [95% CI]	*p*-value
Age, years, mean (SD)	65.9 (10.2)	56.4 (13.6)	**<10^{-3}**	1.06 [1.02-1.09]	0.003
Female sex (%)	54.5	80.3	**<10^{-3}**	0.29 [0.14-0.64]	0.002
Disease duration, mean (SD), years Available data, n (%)	15.4 (10.7) 33 (100)	12.2 (9.9) 1391 (94.8)	0.74	-	-
Weight, mean (SD), kg Available data, n (%)	73.7 (13.3) 31 (93.9)	69.7 (16.1) 1236 (84.2)	0.17	-	-
Family history of cardiovascular disease (%) Available data, n (%)	0 31 (93.9)	3.7 1431 (97.5)	0.28	--	-
Personal history of cardiovascular disease (%) Available data, n (%)	45.5 33 (100)	18.5 1461 (99.5)	**<10^{-3}**	4.10 [1.90-8.83]	<10^{-3}
Type 2 diabetes mellitus (%) Available data, n (%)	9.1 33 (100)	8.4 1461 (99.5)	0.89	-	-
Arterial hypertension (%) Available data, n (%)	45.5 32 (97.0)	30.6 1459 (99.4)	**0.048**	1.40 [0.61-3.19]	0.43
Smoking (%) Available data, n (%)	18.2 33 (100)	21.7 1434 (97.7)	0.63	-	-
Hypercholesterolaemia (%) Available data, n (%)	36.7 30 (90.9)	18.3 1327 (90.4)	**0.01**	1.68 [0.73-3.83]	0.22
No. of cardiovascular risk factors, mean (SD), n (%)	2.5 (0.8)	1.7 (1.1)	0.004	-	-
RF positivity (%) Available data, n (%)	88.9 27 (81.8)	76.6 1280 (87.2)	0.14	-	-
ACPA positivity (%) Available data, n (%)	88.9 27 (81.8)	79.5 1204 (82.0)	0.23	-	-
Initial CRP level (mg/l) Available data, n (%) Mean (SD) Median (min-max)	 29 (82.9) 16.6 (14.5) 13.5 (1-50)	 1299 (88.5) 23.7 (32.8) 12.0 (0-279)	 0.26	-	-
Initial DAS28-ESR, mean (SD) Available data, n (%)	5.1 (1.4) 29 (82.9)	5.1 (1.3) 1207 (82.2)	0.83	-	-
Initial DAS28-CRP, mean (SD) Available data, n (%)	4.9 (1.4) 23 (69.7)	4.8 (1.2) 995 (67.8)	0.60	-	-
Previous bDMARD, mean (SD) Available data, n (%)	2.3 (1.2) 26 (78.8)	2.2 (1.1) 1235 (84.1)		-	-
DMARDs combination (%) TCZ+MTX TCZ + LFN TCZ+HCQ TCZ+SSZ	51.6 88.2 11.8 - -	60.0 82.6 13.7 3.8 2.7	0.32	- -	
Initial treatment with GC (%) Available data, n (%)	72.7 33 (100)	68.4 1464 (99.7)	0.60	-	-
Dose of GC, mean (SD), mg/day Available data, n (%)	12.8 (9.1) 33 (100)	10.1 (7.2) 1452 (98.9)	0.16	1.04 [0.99-1.08]	0.06

MACCE: major adverse cardiac and cerebrovascular event; OR: odds ratio; 95% CI: 95% confidence interval; ACPA: anti-citrullinated protein antibodies; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; bDMARD: biological disease-modifying anti-rheumatic drug; sDMARD: synthetic DMARD; RF: rheumatoid factor; TCZ: tocilizumab; MTX: methotrexate; LFN: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; GC: glucocorticoids.

mia (p=0.01) and number of cardiovascular risk factors (p=0.004) (Table II). Other associated factors were weight, RF positivity and dose of GCs (mg/day). Because of many missing data for weight and RF positivity, we excluded these two factors from the multivariate analysis. After logistic regression, probability of MACCE remained associated with age (OR=1.06 [95% CI 1.02–1.09], p=0.003) and history of cardiovascular disease (4.10 [1.90–8.83], $p<10^{-3}$). Probability of MACCE was still reduced with female sex (OR=0.29 [95% CI 0.14–0.64], p=0.002) and GC dose was no longer significantly associated (1.04 [0.99–1.08], p=0.06). No significant association was found with RA disease activity, even in sensitivity analyses by additional logistic regression models, including either baseline

Table III. Change in cholesterol levels for REGATE registry patients during follow-up.

Change	TC	LDL-C	HDL-C
ΔM0-M3			
Available data, n (%)	415 (32.2)	351 (27.2)	364 (28.2)
Mean (SD), g/l	0.27 (0.50)	0.18 (0.41)	0.06 (0.24)
Percentage	15.4	18.9	13.4
ΔM0-M6			
Available data, n (%)	314 (23.5)	274 (20.5)	283 (21.2)
Mean (SD), g/l	0.15 (0.57)	0.10 (0.46)	0.03 (0.23)
Percentage	10.3	14.0	10.5
ΔM0-M12			
Available data, n (%)	257 (19.2)	222 (16.6)	224 (16.8)
Mean (SD), g/l	0.11 (0.63)	0.03 (0.49)	0.04 (0.22)
Percentage	8.6	7.3	10.5

ΔM0-M3: change from month 0 to month 3; ΔM0-M6: change from month 0 to month 6; ΔM0-M12: change from month 0 to month 12; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

DAS28, baseline DAS28-CRP, baseline CRP, average DAS28 during follow-up, and average DAS28-CRP during follow-up (in addition to the variables included in the main multivariate model cited in Table II, *i.e*. gender, age, history of hypertension, history of cardiovascular disease, dyslipidaemia and corticosteroid dose).

Impact on cholesterol levels

Data on changes in cholesterol levels from baseline to 3 months (M3), 6 months (M6) and 1 year (M12) for all RA patients included in the REGATE registry are in Table III. Levels of all cholesterol variables investigated were increased at 3 months after the initiation of TCZ. Moreover, for 27.5% of RA patients, the LDL-C level was >1.6 g/l at M3 even though levels were normal before the introduction of TCZ. At M6 and M12, the LDL-C level was >1.6 g/l for 21.3% and 17.2% of RA patients. In all, 15.2% of RA patients in the REGATE registry had an increase >30% in the atherogenic index (AI) (TC/HDL-C ratio) at M6, and no association was found with the occurrence of MACCEs (observed in 2.2% of patients with stable AI and 2.1% of patients with increased AI; p=0.61).

Discussion

From the analysis of data from the REGATE registry, the incidence of major cardiovascular events (MACCEs) in current practice among RA patients receiving TCZ was 0.63/100 PYs. No case of cardiovascular death or heart failure was reported. The incidence was 0.41/100 PYs for ischaemic strokes and 0.21/100 PYs for cardiac ischaemia. Predictors of MACCEs were age, female sex and history of cardiovascular disease. We found an early (3-month) increase in levels of all cholesterol variables studied: TC, HDL-C, LDL-C after TCZ initiation.

Despite unfavorable changes in lipid profiles, the global CVD risk with TCZ is comparable to other biologics (12). Cardiovascular safety of TCZ is similar to that of other biologic agents. Two other French registries have been implemented with the same method as the REGATE registry, the ORA and AIR-PR registries, concerning treatment with abatacept and rituximab, respectively. In the ORA registry, with a total exposure of 4912 PYs, the incidence of MACCEs was 0.58/100 PYs after a follow-up of 2 years, close to the 0.63/100 PYs observed in the REGATE registry. In the AIR-PR registry, the incidence of MACCEs after 2 years of follow-up (10,545 PYs) was 0.56/100 PYs.

The incidence of MACCEs was described in analysis of cumulative safety data of TCZ from five phase III clinical trials. Concerning cardiovascular safety, our results are consistent with previous studies. Schiff *et al*. analysed the cumulative safety data for TCZ from five phase III clinical trials, two ongoing extension trials and one clinical pharmacological study (13). This analysis included 4009 RA patients who received at least one dose of TCZ with total exposure of 9414 PYs. The incidence of myocardial infarction was 0.25/100 PYs, close to the 0.21/100 PYs observed in the REGATE registry. The rate of stroke was 0.19/100 PYs. In a large US cohort of 9218 RA patients receiving TCZ, the incidence was 0.52/100 PYs for hospitalisation for ischaemic stroke or myocardial infarction. The median duration of follow-up was 0.9 years (14). For RA patients receiving an anti-tumour necrosis factor (TNF) agent, 8,670 patients were included in the British registry BRSBR with a total exposure of 13,233 PYs. The incidence of myocardial infarction was 0.48/100 PYs (15). In a US cohort study, 18,810 RA patients initiating treatment with an anti-TNF agent were included with a mean follow-up of 0.9 years and a maximal observational period of 4.5 years(14). The incidence was 0.59/100 PYs for hospitalisation for ischaemic stroke or myocardial infarction, close to the 0.63/100 PYs observed in the REGATE registry. In the ENTRACTE study including 3,080 RA patients with a follow-up of 3.2 years, the occurrence of MACCEs did not significantly differ between RA patients receiving TCZ *versus* etanercept (hazard ratio =1.05 [95% CI 0.77–1.43]), whereas TC, LDL-C, HDL-C and TG levels were increased significantly with TCZ *versus* etanercept (16). This absence of difference on cardiovascular events between etanercept and TCZ was also reported using administrative healthcare databases in Italy. Using a validated algorithm, Generali G *et al*. compared acute cardiovascular events in 1086 RA patients treated with ETN and 666 under TCZ (17). The risk of myocardial infarction and stroke were not different between the two bDMARDs with respectively hazard ratios of 0.39 (CI95% 0.15–1.06) and 1.44 (CI95% 0.24–8.68) even after adjustment for pre-specified confounders (sex, age, disease duration, methotrexate (MTX), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), number of previous biologics, presence of hypertension, dyslipidaemia, diabetes and previous CV events). Thus, TCZ did not seem to be

associated with increased cardiovascular risk in RA patients.

As clearly stated in most international recommendations, the management of cardiovascular risk in patients with RA should primarily be based on the optimal control of disease activity, and the appropriate use of the available therapies remains the most positively impacting factor a rheumatologist can offer his patient (18). This aspect could not be appropriately investigated in our study, because our patients had a similar but very specific profile, *i.e.* a certain severity of disease that required the use of TCZ. The global – presumably positive – impact of other DMARDs on the CV risk could thus not be properly evaluated, with even an apparently –although not significant- observed protective effect of TCZ monotherapy versus combination with a csDMARD. Indeed, systemic inflammation caused by disease activity undoubtedly plays a role in the increased cardiovascular risk observed in RA patients (19). However, our analyses did not reveal an association between levels of acute phase reactants (CRP) at the time TCZ was initiated, or the baseline disease activity. This might be explained by the very partial information given by the punctual assessments made in a patient at the time he was started on TCZ (presumably during a disease flare, after a certain past history of disease and possibly multiple DMARDs). In addition, there is also increasing evidence indicating a close link between MACCEs risk and insulin resistance. Moreover, IL-6 is closely related to this insulin resistance even in RA patients with no diabetes (20). Unfortunately, we could not examine correctly the effect of TCZ on insulin resistance and the association with MACCEs since we did not have this direct information about insulin resistance in RA patients included and followed in the REGATE registry, as these patients were treated in routine clinical practice, without specific or additional biologic assessments made. We could only investigate this aspect by examining the association between MACCEs and the presence of diabetes mellitus, which was a systematically collected item. However, we did not find any significant association between the occurrence of a MACCE and the presence of diabetes in our patients.

In our study, it would appear that dose of GC increased the probability of MACCEs on multivariate analysis, with an increase of 4% in cardiovascular risk for 1mg/day (OR=1.04 [95% CI 0.99–1.08], p=0.06), but did not reach statistical significance probably because of lack of power with the small number of MACCEs.

Concerning changes in cholesterol levels in RA patients receiving TCZ, our results are consistent with those of previous studies, notably cumulative safety data from five controlled and extension studies (6-10). In these studies, increase in LDL-C level was >1.6 g/l after 6 months of treatment with TCZ in 3.1% to 18% of RA patients (in 21.3% of our patients). Moreover, in the OPTION (6) and TOWARD (7) studies, the authors found the atherogenic index increased >30% after 6 months of treatment with TCZ in 17% and 12% of RA patients, respectively; in our study an increase >30% was observed in 15.2% of patients. In RA patients receiving MTX or an anti-TNF agent, most of studies also describe also an increase in all cholesterol levels but generally no increase in atherogenic index (21-23).

The main strength of our study was the number of RA patients followed up in the REGATE registry, which allowed us to obtain data on cardiovascular safety in RA patients receiving TCZ in current practice. Our study has several limitations, especially data available for cholesterol components. However, more than 200 dosages were analysed. Another limitation was the low number of MACCEs, which could disallow identification of risk factors associated with MACCE because of lack of power. However, this is a reassuring element for the safety of TCZ.

Conclusion

Our study of the REGATE registry provides reassuring data concerning the cardiovascular safety of treatment with TCZ in RA patients in current practice. The rate of major cardiovascular events is in the range observed with other biologics and is also close to those observed in previous studies concerning TCZ in extensions of pivotal studies. We confirmed the impact of treatment with TCZ on changes in cholesterol levels. However, the treatment does not seem to be associated with an increase in cardiovascular complications.

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