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Comparison of the risks of hospitalisation for cardiovascular events in patients with rheumatoid arthritis treated with tocilizumab and etanercept

E. Generali[1], G. Carrara[2], C. Selmi[1,3], S. Verstappen[4], A. Zambon[5], A. Bortoluzzi[6], E. Silvagni[6], C.A. Scirè[2,6]

[1]Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Rozzano, Italy;
[2]Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy;
[3]BIOMETRA Department, University of Milan, Italy;
[4]Arthritis Research UK Centre for Epidemiology, The University of Manchester, UK;
[5]Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Milan, Italy;
[6]Rheumatology Unit, Department of Medical Sciences, University of Ferrara, Italy.

*Elena Generali, MD, PhD**
*Greta Carrara, Stat.**
Carlo Selmi, MD, PhD
Suzanne Verstappen, PhD
Antonella Zambon, PhD
Alessandra Bortoluzzi, MD, PhD
Ettore Silvagni, MD
Carlo Alberto Scirè, MD, PhD

**These authors contributed equally.*

Please address correspondence to:
Carlo A. Scirè, MD, PhD,
Epidemiology Unit,
Italian Society for Rheumatology
Via Turati 40,
20121 Milano, Italy.
E-mail: c.scire@reumatologia.it

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ABSTRACT

Objective. *To verify if tocilizumab (TCZ) is associated with an increased risk of cardiovascular (CV) events compared with etanercept (ETN) in rheumatoid arthritis (RA).*

Methods. *This is a retrospective cohort study on administrative healthcare databases (AHD) in Italy. Patients were identified using a validated algorithm based on AHD. Exposure to specific drugs was estimated by the drug prescription recorded in the AHD. The occurrence of acute CV events (myocardial infarction, stroke, other CV events) was derived from the hospital discharge forms. The association between TCZ or ETN and CV events was estimated using competing risk models, adjusting for pre-specified confounders.*

Results. *We identified 1,752 subjects with RA, 1,086 treated with ETN and 666 with TCZ. TCZ did not increase the overall risk of acute CV events, even when adjusted for pre-specified confounders (hazard ratio HR 0.95, 95% confidence interval 95%CI 0.54–1.66), specifically of acute myocardial infarction (HR 0.39, 95%CI 0.15–1.06), stroke (HR 1.44, 95%CI 0.24–8.68) or other CV event (1.07, 95%CI 0.59–1.92).*

Conclusion. *RA patients with TCZ do not have a medium-term excess of CV risk in patients compared with ETN.*

Introduction

Rheumatoid arthritis (RA) is associated with an increased incidence of atherosclerosis leading to myocardial infarction and stroke, accounting for a 35–50% excess mortality (1-4). Biologic disease-modifying anti-rheumatic drugs (DMARDs) targeting tumour necrosis factor (TNF)-α or interleukin (IL)-6 may influence the RA-associated cardiovascular (CV) risk (5), but available data are limited by the events low incidence, limiting the feasibility of prospective studies.

While coronary heath disease (CHD) genetic studies and experimental models suggest that IL-6 is pivotal in atherosclerosis and CV disease development, suggesting that IL-6 blockade might reduce CV risk (6, 7), tocilizumab (TCZ) was associated with an increase in plasma lipid levels, suggesting a potential increase in CV risk (8). To understand the effect of TCZ on the RA-associated CV risk in clinical practice and to test the hypothesis that TCZ is associated with an increased risk of acute CV events compared with etanercept (ETN), we analysed administrative healthcare databases (AHD) of a Northern Italian region.

Methods

Study design

This is a retrospective cohort study on AHD of Lombardy Region, Italy (>10,000,000 inhabitants).

Data

Data included were retrieved between 1st of January 2010 and 31st of December 2013 by record linkage from the following AHD: demographics, pharmacy, certification for chronic diseases (exemption), outpatient services, hospital discharge forms (HDF). From these sources, the following variables were extracted: birth date, gender, death or embankment date, drug delivery (using anatomic-therapeutic chemical classification codes), date and amount of drug prescription, exemption codes, date of exemption, codes and dates of each outpatient services and international classification of diseases (ICD)-9-CM diagnoses, diagnostic-related groups (DRG), and start-end dates for every hospitalisation. The access to the data was granted by the General Directorate of Health for the purpose of the RECord linkage on Rheumatic Diseases (RECORD) study protocol of analysis, in accordance with national ethical requirements.

Population

Patients with RA were identified through a validated algorithm combining exemption for RA, outpatient drug prescriptions and HDF (9). Patients with RA starting treatment with TCZ or ETN for the first time were included in this study. The exposure to specific drugs was estimated by the drug prescription recorded in the AHD: patients with at least one TCZ prescription entered in TCZ cohort, patients with at least one ETN prescription entered in ETN cohort.

Exposure

A patient was considered exposed to the treatment from the first prescription until the last one plus six months, in order to consider the coverage period of drug also after its withdrawal. Temporary stops were allowed, regardless of their duration. Patients who switched from ETN to TCZ or vice versa were assigned to TCZ in main analyses and to ETN in sensitivity analyses. Time-dependent exposure was also considered.

Outcome

Hospitalisation/death for acute CV events during the exposition period were evaluated using HDF using relevant ICD-9-CM and DRG codes respectively: 431*, 433-435* and 014, 015 for acute cerebrovascular events, 410*, 411*, 413* and 121-123, 140 for acute coronary heart disease, 415.1, 415.11, 415.19, 426.0, 426.12-426.13, 426.51-426.52, 426.54, 427.1, 427.4, 427.41-427.42, 427.5, 428*, 430*-436*, 441.0*, 441.1, 441.3, 453.0, 453.2-453.3, 453.8, 785.51 and 078, 087, 106, 110-114, 127-128, 138-139, 515, 518, 524-525, 528, 535-536, 547-559 for other acute CV events.

Statistical methods

The association between TCZ or ETN exposure and hospitalisation/death for CV events was assessed by survival models for competing risks. Results were presented as hazard ratios (HR) and 95% confidence intervals (CI), crude and adjusted 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). The sample size and the number of events were sufficient to estimate a 2-fold increase (or decrease) of the risk of CV events in the primary outcome measure, setting alpha = 0.05 and beta = 0.80. In primary analyses, patients with prescription for both TCZ and ETN entered the TCZ cohort. In order to explore the robustness of results, sensitivity analyses evaluating the impact of unmeasured confounding, also applying time-dependent exposure models, were performed (10). Analyses were performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Table I. Demographic, clinical and therapeutic features of the RA treatment cohorts.

	Etanercept (n=1086)	Tocilizumab (n=666)	*p*-value
Female, n (%)	767 (70.6%)	545 (81.8%)	<0.001
Age mean, years (SD)	55.3 (13.2)	56.8 (12.6)	0.027
Disease duration, <1 year, n (%)	92 (8.5%)	71 (10.7%)	<0.001
Disease duration, 1-2years, n (%)	254 (23.4%)	101 (15.2%)	
Disease duration, 3-5 years, n (%)	158 (14.5%)	84 (12.6%)	
Disease duration, >5 years, n (%)	582 (53.6%)	410 (61.6%)	
Previous biologic therapy* median, (IQR)	0 (0-1)	1 (0-2)	<0.001
NSAIDs use, n (%)	690 (63.5%)	485 (72.8%)	<0.001
Concurrent MTX use at start, n (%)	623 (57.4%)	365 (54.8%)	0.294
Oral steroids use, n (%)	639 (58.8%)	478 (71.8%)	<0.001
Hypertension**, n (%)	188 (17.3%)	126 (18.9%)	0.394
Diabetes**, n (%)	98 (9%)	54 (8.1%)	0.509
Dyslipidaemia**, n (%)	173 (15.9%)	125 (18.8%)	0.125
Previous myocardial infarction, n (%)	28 (2.6%)	12 (1.8%)	0.291
Previous stroke, n (%)	17 (1.6%)	17 (2.6%)	0.146
Previous acute CV event (other), n (%)	55 (5.1%)	54 (8.1%)	0.010
Any previous CV event, n (%)	69 (6.4%)	62 (9.3%)	0.022

*Biologic therapy (rituximab, abatacept, infliximab, adalimumab, certolizumab pegol, golimumab) prescribed before entering the cohort.
**Defined by having disease specific exemptions or specific drug prescriptions before entering the cohort.

Results

A total of 1,086 patients with RA starting with ETN (median exposure 616 days, interquartile range (IQR) 292-1125, mean (standard deviation - SD) 721(460) and 666 with TCZ (median exposure 541.5 days, IQR 301-967, mean (SD) 652 (400)) were included in the analyses. Their demographic, clinical and therapeutic features are illustrated in Table I.

In total, 22 CV events in 1,003 person-years were observed in the TCZ cohort and 36 CV events in 1,835 person-years were observed in the ETN cohort with incidence rate ratio 21.9 (95%CI 14.4–33.3) and 19.6 (95%CI 14.1–27.2) per 1,000 person-years, respectively.

The results of the crude competing risk model estimating the CV risk, using ETN as a reference, show that TCZ is not associated with a statistically significant increase of the risk of CV events (HR 1.05, 95%CI 0.62–1.78; *p*=0.848). With regard to specific outcomes, TCZ did not show any significant relative increased risk of myocardial infarction (HR 0.43, 95%CI 0.14–1.27; *p*=0.127), stroke (HR 2.53, 95%CI 0.61–10.52; *p*=0.202) or any other CV event (HR 1.18, 95%CI 0.68–2.03; *p*=0.564). When adjusting for pre-specified confounders, TCZ did not show significant relative increase of the risk of overall acute CV events (HR 0.95, 95%CI 0.54–1.66; *p*=0.860) and, when looking at specific outcomes, no increased risk of acute myocardial infarction (HR 0.39, 95%CI 0.15–1.06; *p*=0.065), stroke (HR 1.45, 95%CI 0.24–8.68; *p*=0.691) and other CV event (HR 1.07, 95%CI 0.59–1.92; *p*=0.823).

In the first sensitivity analysis, in which patients with prescription for both TCZ and ETN entered the ETN cohort, we did not find any substantial difference, with a general CV HR of 0.92 (95%CI 0.52–1.62). Time-dependent exposure confirmed a general CV fully adjusted HR of 1.21 (95%CI 0.72–2.03).

A second sensitivity analysis, exploring the hypothesis that unmeasured confounders could have biased the observed HR, indicates that a theoretical increase of the CV risk associated with TCZ would be possible only in the presence of a complete unbalance of unmeasured confounders carrying a strong protective effect (risk ratio <0.3) against CV events (Fig. 1).

Discussion

Myocardial infarction and stroke represent a significant cause of morbidity and mortality in RA. We herein report

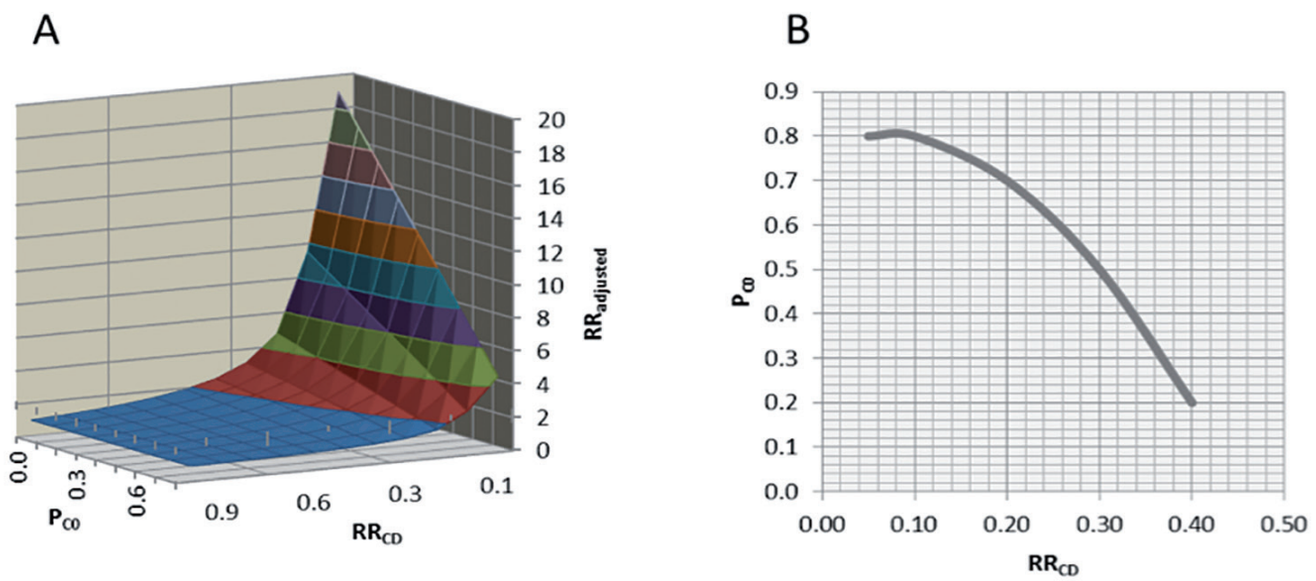

Fig. 1. Sensitivity analysis and external adjustment for unmeasured confounders. The analysis aims to disprove the finding of no increase CV risk associated with TCZ, hypothesising that protective unmeasured confounders associated with TCZ masked the true associations between TCZ and CV events. P_{C0}: prevalence of a hypothetic protective unmeasured confounder in the control group (ETN). RR_{CD}: risk ratio of CV outcome. RR: "True" or fully adjusted exposure relative risk.

Panel **A** reports the relative risk adjusted for measured and unmeasured confounders, as a function of a range of possible values of prevalence of the factor in the ETN group (P_{C0}) assuming 100% prevalence in the TCZ group (P_{C1}=1), and a range of protective effect (the lower RR the higher protective effect and therefore potential influence).

Panel **B**. All the points under the curve represent the combinations of P_{C0} and RR_{CD}, assuming P_{C1} = 1 that would have led to a statistically significant increase of the risk of CV associated with TCZ, based on the power of the study sample (minimum HR 2.1).

the risk of acute CV events in a representative sample of the general population of RA patients exposed to ETN or TCZ. We observed that TCZ did not increase the overall risk of acute CV events compared to ETN, and similarly of myocardial infarction, stroke or other acute CV events including heart failure. These results should be interpreted in light of the complex interplay between risk factors and CV risk observed in RA. CV disease accounts for approximately 50% of the excess mortality of RA, being strongly related to chronic inflammation with a minor contribution of traditional CV risk factors (11, 12). RA and atherosclerosis share many pathogenetic pathways, as TNF-α can alter the endothelial structure, and lead to the remodelling of smooth muscle cells and rupture of atherosclerotic plaques (13), while IL-6 significantly contributes to the overall endothelial activation and induces very-low-density lipoprotein receptor (12). Data on the genetic susceptibility to CHD and from experimental studies point to IL-6 as crucial to atherosclerosis development (6), and a polymorphism of IL-6 gene that does mimic TCZ action was found not to increase CV mortality in RA patients (15). Based on these observations, anti-rheumatic therapies are expected to impact the CV risk associated with RA (16, 17). Biologic DMARDs reduce inflammation, and modulate serum lipid levels (18) while ETN acts on plasma high-density lipoprotein, total cholesterol and triglycerides (19) improving the endothelial function and ultimately impacting survival (20). Targeting IL-6 has a theoretical potential in both chronic inflammation and atherosclerosis, however, during earlier treatment phases, TCZ can induce the increase of lipid levels in a subgroup of patients but these decrease below baseline levels after 3 months (21).

Based on our results, the 'net influence' of TCZ is not toward an increase of CV risk in RA. However we should consider that an unbalanced distribution of unmeasured risk factors (*e.g.* smoking, obesity) could mask an increase CV risk for TCZ. On the other hand, as also shown in our sample, TCZ was commonly prescribed to more severe cases of RA potentially inflating the influence of this drug and CV events.

In order to disprove our findings, we performed a sensitivity analysis accounting for additional confounding factors not considered, and show that the probability that these factors revert the conclusions of our study is negligible. This is also particularly true given that a channelling bias leading to lower probability of TCZ prescription in patient with different CV risk history or risk factors might have taken place.

One of the limitations of our study was that we could not verify CV events recorded in database nor identify CV disease not leading to hospitalisation or CV events not recorded in HDF. More importantly, despite the inclusion of a large population based sample, the number of events is still low, and the study is powered to detect almost two-fold increase or decrease of the risk, while even lower variations might still be clinically significant.

In conclusion, we show that TCZ treatment is not associated with an increased risk of CV events compared to ETN. The clinical implications of this observation include the possibility that TCZ may be used as first-line biologic in RA at least with the same CV safety profile of ETN.

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References

1. GOODSON N, MARKS J, LUNT M, SYMMONS D: Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. *Ann Rheum Dis* 2005; 64: 1595-601.
2. HUMPHREYS JH, WARNER A, CHIPPING J *et al*.: Mortality trends in patients with early rheumatoid arthritis over 20 years: results from the Norfolk Arthritis Register. *Arthritis Care Res* (Hoboken) 2014; 66: 1296-301.
3. FRANKLIN J, FARRAGHER TM, LUNT M *et al*.: Excess risk of hospital admission for cardiovascular disease within the first 7 years from onset of inflammatory polyarthritis. *Ann Rheum Dis* 2010; 69: 1660-4.
4. VAN DEN HOEK J, ROORDA LD, BOSHUIZEN HC, TIJHUIS GJ, DEKKER J, VAN DEN BOS GA, NURMOHAMED MT: Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study. *Clin Exp Rheumatol* 2016; 34: 813-19.
5. LIM DT, CANNELLA AC, MICHAUD KD, MIKULS TR: Cardiovascular risk and the use of biologic agents in rheumatoid arthritis. *Curr Rheumatol Rep* 2014; 16: 459.
6. INTERLEUKIN-6 RECEPTOR MENDELIAN RANDOMISATION ANALYSIS CONSORTIUM, HINGORANI AD, CASAS JP: The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* 2012; 379: 1214-24.
7. GUALTIEROTTI R, INGEGNOLI F, GRIFFINI S, GROVETTI E, MERONI PL, CUGNO M: Prothrombotic biomarkers in patients with rheumatoid arthritis: the beneficial effect of IL-6 receptor blockade. *Clin Exp Rheumatol* 2016; 34: 451-8.
8. JONES G, SEBBA A, GU J *et al*.: Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010; 69: 88-96.
9. CARRARA G, SCIRE CA, ZAMBON A *et al*.: A validation study of a new classification algorithm to identify rheumatoid arthritis using administrative health databases: case-control and cohort diagnostic accuracy studies. Results from the RECord linkage On Rheumatic Diseases study of the Italian Society for Rheumatology. *BMJ Open* 2015; 5: e006029.
10. SCHNEEWEISS S: Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006; 15: 291-303.
11. DEL RINCON ID, WILLIAMS K, STERN MP, FREEMAN GL, ESCALANTE A: High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; 44: 2737-45.
12. CHOY E, GANESHALINGAM K, SEMB AG, SZEKANECZ Z, NURMOHAMED M: Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. *Rheumatology* (Oxford) 2014; 53: 2143-54.
13. SATTAR N, MCCAREY DW, CAPELL H, MC INNES IB: Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003; 108: 2957-63.
14. HASHIZUME M, YOSHIDA H, KOIKE N, SUZUKI M, MIHARA M: Overproduced interleukin 6 decreases blood lipid levels via upregulation of very-low-density lipoprotein receptor. A*nn Rheum Dis* 2010; 69: 741-6.
15. IBRAHIM I, MCALLISTER K, PLANT D *et al*.: Investigation of an interleukin-6 receptor gene polymorphism (rs2228145) as a predictor of cardiovascular mortality in inflammatory polyarthritis: results from the Norfolk Arthritis Register. *Ann Rheum Dis* 2014; 73: 787-8.
16. GREENBERG JD, KREMER JM, CURTIS JR *et al*.: Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 576-82.
17. NARANJO A, SOKKA T, DESCALZO MA *et al*.: Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* 2008; 10: R30.
18. JACOBSSON LT, TURESSON C, GULFE A *et al*.: Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 1213-8.
19. DAIEN CI, DUNY Y, BARNETCHE T, DAURES JP, COMBE B, MOREL J: Effect of TNF inhibitors on lipid profile in rheumatoid arthritis: a systematic review with meta-analysis. *Ann Rheum Dis* 2012; 71: 862-8.
20. MORGAN CL, EMERY P, PORTER D *et al*.: Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data. *Rheumatology* (Oxford) 2014; 53: 186-94.
21. SCHIFF MH, KREMER JM, JAHREIS A, VERNON E, ISAACS JD, VAN VOLLENHOVEN RF: Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011; 13: R141.