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

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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 heart 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), separately: 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.

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.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Etanercept (n=1086)</th>
<th>Tocilizumab (n=666)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>767 (70.6%)</td>
<td>545 (81.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age mean, years (SD)</td>
<td>55.3 (13.2)</td>
<td>56.8 (12.6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Disease duration, &lt;1 year, n (%)</td>
<td>92 (8.5%)</td>
<td>71 (10.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration, 1-2 years, n (%)</td>
<td>254 (23.4%)</td>
<td>101 (15.2%)</td>
<td>0.065</td>
</tr>
<tr>
<td>Disease duration, 3-5 years, n (%)</td>
<td>158 (14.5%)</td>
<td>84 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>Disease duration, &gt;5 years, n (%)</td>
<td>582 (53.6%)</td>
<td>410 (61.6%)</td>
<td></td>
</tr>
<tr>
<td>Previous biologic therapy* median, (IQR)</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAIDs use, n (%)</td>
<td>690 (63.5%)</td>
<td>485 (72.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concurrent MTX use at start, n (%)</td>
<td>623 (57.4%)</td>
<td>365 (54.8%)</td>
<td>0.294</td>
</tr>
<tr>
<td>Oral steroids use, n (%)</td>
<td>639 (58.8%)</td>
<td>478 (71.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension**, n (%)</td>
<td>188 (17.3%)</td>
<td>126 (18.9%)</td>
<td>0.394</td>
</tr>
<tr>
<td>Diabetes**, n (%)</td>
<td>98 (9%)</td>
<td>54 (8.1%)</td>
<td>0.509</td>
</tr>
<tr>
<td>Dyslipidaemia**, n (%)</td>
<td>173 (15.9%)</td>
<td>125 (18.8%)</td>
<td>0.125</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>28 (2.6%)</td>
<td>12 (1.8%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>17 (1.6%)</td>
<td>17 (2.6%)</td>
<td>0.146</td>
</tr>
<tr>
<td>Previous acute CV event (other), n (%)</td>
<td>55 (5.1%)</td>
<td>54 (8.1%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Any previous CV event, n (%)</td>
<td>69 (6.4%)</td>
<td>62 (9.3%)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*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 increase of the risk of 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).

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
CV risk in ETA- vs. TCZ-treated RA patients / E. Generali et al.

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.
Acknowledgments
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References