ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 2, February 2015, pp 372–380
DOI 10.1002/art.38920

An Evaluation of Risk Factors for Major Adverse Cardiovascular Events During Tocilizumab Therapy

Vijay U. Rao,[1] Andrey Pavlov,[2] Micki Klearman,[1] David Musselman,[1] Jon T. Giles,[3] Joan M. Bathon,[3] Naveed Sattar,[4] and Janet S. Lee[5]

Objective. **To evaluate associations between lipid levels, inflammation, and rheumatoid arthritis (RA) disease activity, at baseline and during treatment, with the risk of major adverse cardiovascular events (MACE) in tocilizumab-treated patients with RA.**

Methods. **In retrospective post hoc analyses, data were pooled for 3,986 adult patients with moderate to severe RA who received ≥1 dose of tocilizumab (4 mg/kg or 8 mg/kg) intravenously every 4 weeks in randomized controlled trials and extension studies. Cox proportional hazards modeling was used to evaluate associations between baseline characteristics and posttreatment changes in laboratory and disease characteristics (week 24) and change in disease activity and laboratory values from baseline to week 24 with the risk of future MACE during extended followup.**

Results. **We identified 50 independently adjudicated cases of MACE during 14,683 patient-years of followup (0.34 MACE cases/100 patient-years). At baseline, age, a history of cardiac disorders, the Disease Activity Score in 28 joints (DAS28), and the total cholesterol:high-density lipoprotein cholesterol ratio were independently associated with MACE in multivariable models ($P < 0.05$ for all). During treatment, a higher DAS28 and higher swollen and tender joint counts at week 24 were associated with future MACE. In separate models, greater reductions in the DAS28 and joint counts from baseline to week 24 were inversely associated with future MACE; changes in lipid parameters were not statistically significantly associated with the risk of MACE.**

Conclusion. **In this population of patients treated with tocilizumab, an association was observed between the baseline total cholesterol:high-density lipoprotein cholesterol ratio and an increased risk of MACE. The risk of MACE while receiving treatment, however, was associated with control of disease activity but not lipid changes. Larger studies are needed to confirm these findings.**

Patients with rheumatoid arthritis (RA) have approximately double the risk of myocardial infarction (MI) and stroke compared with that in the general population (1,2). Several studies suggest that the increased incidence of cardiovascular disease (CVD) in RA is not completely explained by traditional CV risk factors such as diabetes mellitus, hypertension, smoking, and dyslipidemia (3–5). Indeed, the HLA–DRB1 shared epitope, higher erythrocyte sedimentation rates (ESRs), and RA comorbidities such as vasculitis and pulmonary disease are associated with an increased risk of CVD-related mortality (4,6). In a population-based incidence cohort of RA patients with high ESRs, those with much lower total cholesterol and low-density lipoprotein

Supported by F. Hoffmann-La Roche Ltd.

[1]Vijay U. Rao, MD, PhD (current address: Franciscan Provider Network, Indiana Heart Physicians, Indianapolis, Indiana), Micki Klearman, MD, David Musselman, MD: Genentech, South San Francisco, California; [2]Andrey Pavlov, PhD: Everest Clinical Research Services, Toronto, Ontario, Canada; [3]Jon T. Giles, MD, MPH, Joan M. Bathon, MD: Columbia University, New York, New York; [4]Naveed Sattar, MD, PhD: University of Glasgow, Glasgow, UK; [5]Janet S. Lee, PhD (current address: LifeTech Research, Edgewater, Maryland): Roche, Nutley, New Jersey.

Dr. Rao was recipient of a Genentech Research Fellowship with salary support during the study. Dr. Klearman owns stock or stock options in Genentech. Dr. Giles has received consulting fees from Genentech (less than $10,000). Dr. Sattar has received speaking fees and consulting fees from Roche for serving on the Steering Committee during the ENTRACTE (Arthritis and Cardiovascular Disease Risk Factors) trial (less than $10,000).

Address correspondence to Micki Klearman, MD, Genentech, 1 DNA Way, Mail Stop 304, South San Francisco, CA 94080. E-mail: klearman.micki@gene.com.

Submitted for publication September 26, 2013; accepted in revised form October 14, 2014.

(LDL) cholesterol levels were paradoxically at increased risk of CVD (7). Thus, further exploration is needed to determine the relative contributions of traditional CVD risk factors, inflammation, and RA disease activity to the risk of major adverse CV events (MACE) in the RA patient population.

Multiple cohort studies suggest a relationship between parameters of RA disease activity and an increased risk of CV events (6,8,9). In fact, the occurrence of CV events appears to be lower in patients who received nonbiologic disease-modifying antirheumatic drugs (DMARDs) (10) and in those who responded to a biologic DMARD compared with those who did not (11). Furthermore, several studies have linked interleukin-6 (IL-6), one of the primary drivers of RA-related inflammation, with the development of coronary heart disease in both patients with RA and the general population (12–15).

Tocilizumab (TCZ) is a humanized monoclonal antibody against the IL-6 receptor (IL-6R) that is approved for the treatment of patients with moderate to severe RA in whom the response to a nonbiologic DMARD was inadequate (16,17). Several randomized, controlled, phase III clinical trials demonstrated the efficacy and safety of TCZ in combination with nonbiologic DMARDs (18–21) or as monotherapy in patients with RA (22–24). Treatment with TCZ results in elevations in mean lipid levels (total cholesterol, high-density lipoprotein [HDL] cholesterol, LDL cholesterol, and triglyceride). Although such elevations are similar to those associated with treatment with other antiinflammatory agents (e.g., tumor necrosis factor α [TNFα] blockers), they are of greater magnitude (24,25). These changes tend to occur within the first few weeks of treatment and remain stable during long-term therapy (26).

The purpose of this analysis was to evaluate whether baseline risk factors (demographic characteristics, lipid levels, inflammation, and RA disease activity) are associated with MACE in patients receiving TCZ and, in particular, whether changes in the levels of lipids and circulating inflammatory markers or changes in RA-specific disease activity measures that occur with TCZ treatment are associated with the risk of subsequent development of MACE.

PATIENTS AND METHODS

Data sources and patient populations. Using post hoc retrospective analyses, we evaluated pooled data for adults with moderate to severe RA who received at least 1 dose of TCZ (4 mg/kg or 8 mg/kg) intravenously every 4 weeks, in combination with methotrexate or other DMARDs or as monotherapy, in registration trials (18–22) and in ongoing extension studies up to the cutoff date of April 1, 2011 (Figure 1). All clinical and laboratory assessments for this analysis were collected in accordance with the study protocol, at regular intervals and at unscheduled visits as appropriate. All blood samples (except those used for evaluation of the ESR) were sent to a central laboratory (Covance Central Laboratory Services) for processing. Assessment of the ESR was performed at each study site using an ESR testing kit supplied by Covance. Blood samples used for the assessment of lipid levels were collected from each patient after an overnight fast.

MACE was defined as definite or probable nonfatal MI, nonfatal stroke, or death caused by CVD. Records from patients with serious adverse events in the Medical Dictionary for Regulatory Activities (version 13.0) System Organ Classes of cardiac, vascular, nervous system, and general disorders were reviewed for potential major adverse CV–related events. Cases were adjudicated in a blinded manner by an independent cardiologist with experience serving on MACE adjudication panels, who confirmed definite cases of MACE. The definitions used are shown in Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38920/abstract.

Statistical analysis. The demographic and baseline characteristics of the patients (e.g., laboratory and RA disease activity measures, medical history) were summarized descriptively for patients with and those without MACE. Given that not all patients were randomly assigned to TCZ at the start of the studies, in this analysis, baseline was defined as the time when the first dose of TCZ was administered.

Cox proportional hazards models were used to evaluate associations between risk factors and time to development of MACE. Associations were expressed in the form of hazard ratios (HRs), and 95% confidence intervals (95% CIs) represented the uncertainty of the estimation. The HR was interpreted as a multiplier of the risk of MACE, corresponding to a 1-unit increase in the predictor. Specific examples of interpretation of the HR are shown in Figures 2–4. Cases of MACE that began before the baseline visit were not counted in this on-treatment analysis.

Patients were evaluated until withdrawal from the study, completion of the study, or the initial occurrence of MACE, whichever occurred first. In the event of multiple occurrences of MACE, only the first was counted. Univariate associations between demographic and baseline disease/laboratory characteristics and time to future MACE were examined by fitting separate models for each variable. Because of the small number of events, limited multivariable modeling was completed and focused on baseline/demographic characteristics that might be important to evaluate in conjunction with posttreatment changes in laboratory and disease characteristics. Selection of baseline variables for the multivariable Cox model was performed with the considerations described here to ensure robustness and validity of the estimates. Highly correlated variables, such as the swollen joint count (SJC), tender joint count (TJC), and Disease Activity Score in 28 joints (DAS28) (27), were not entered together. The best score method (28) was used to select between such variables. Forward, backward, and stepwise variable selection methods were then used to verify the stability of selection.

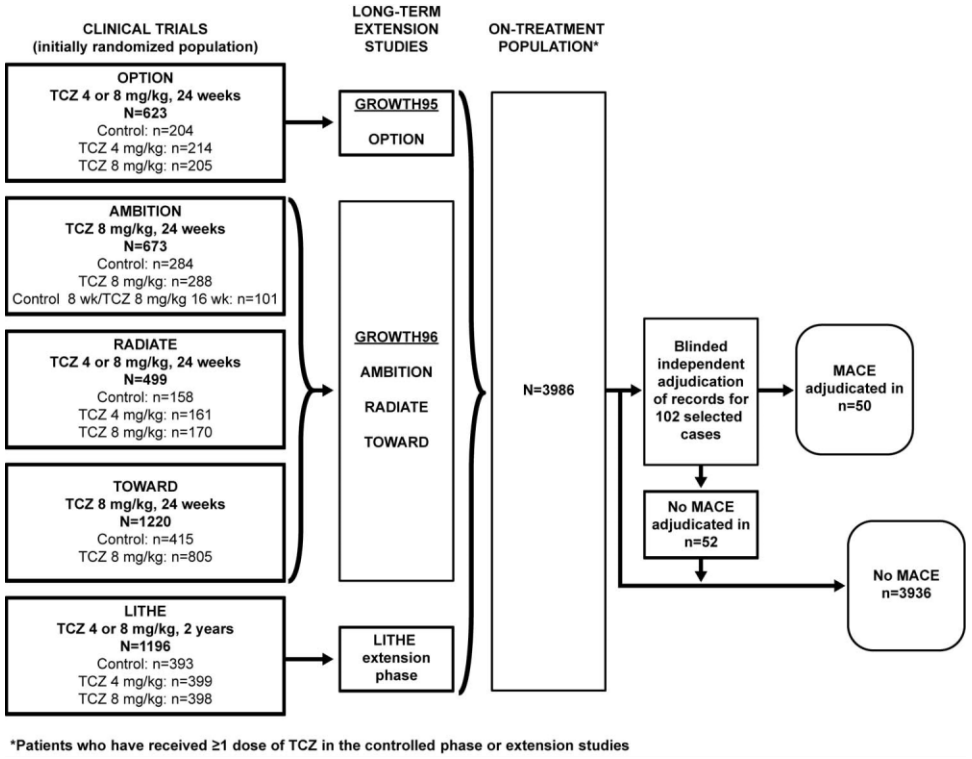

Figure 1. Data sources and patient disposition. OPTION = Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders study; TCZ = tocilizumab; AMBITION = Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension; RADIATE = Research on Tocilizumab Determining Efficacy after Anti-TNF Failures; MACE = major adverse cardiovascular event; TOWARD = Tocilizumab in Combination with Traditional DMARD Therapy; LITHE = The Tocilizumab Safety and the Prevention of Structural Joint Damage study.

Changes in the predictors of MACE from baseline to week 24 and time to future development of MACE were evaluated after adjusting for age and baseline values to show how treatment-initiated changes were associated with future MACE. For these analyses, only patients with exposure after the week 24 assessment were considered (i.e., patients who had MACE before week 24 [n = 8] or who had withdrawn or completed the study by week 24 [n = 220] were excluded). Thus, 42 MACE cases that occurred after week 24 were considered. Additionally, patients with missing data for a week 24 variable were excluded from the analysis of that variable. Change from baseline was always calculated as the score at week 24 minus the score at baseline; hence, negative-change scores indicated decreases in the predictor value over time, whereas positive-change scores indicated increases in the predictor value over time. The HRs in these analyses correspond to a 1-unit increase in the predictor value from baseline (e.g., worsening joint counts or total cholesterol levels).

For all analyses of predictors, unadjusted *P* values less than 0.05 were considered significant. Sensitivity analyses, including 5 additional "probable" MACE cases, were conducted to evaluate the stability of the results. Analyses using laboratory and disease activity predictors observed at week 24 were conducted to further explore the associations between the absolute values of these parameters and future MACE. Such analyses are supportive of the baseline analysis in that they also explore whether the absolute levels of laboratory and disease activity parameters after TCZ exposure are predictive of future MACE.

RESULTS

Exposure and disposition. For this analysis, the total duration of TCZ exposure was 14,683 patient-years. The mean ± SD duration of treatment was 3.68 ± 1.79 years (median 4.54 years), and the maximum length of TCZ exposure was 5.7 years. Independent adjudication of 102 potential cases of MACE in 3,986 patients treated with TCZ, conducted in a blinded manner, confirmed 50 cases, for a rate of 3.4/1,000 patient-years. Characteristics of the patients with and those without MACE at baseline are shown in Table 1. For the 50 patients with MACE, the median number of days from administration of the first dose of TCZ to development of MACE was 680 (range 29–1,792). MACE was observed throughout the exposure period, with no obvious time trends.

Table 1. Baseline characteristics of the patients with RA*

Characteristic	MACE (n = 50)	No MACE (n = 3,936)
Demographics and health status		
Age, years	61.2 ± 10.2	52.1 ± 12.5
Female, no. (%)	40 (80.0)	3,232 (82.1)
Body mass index, kg/m^2	28.2 ± 5.2	27.6 ± 6.3
Family history of CHD, no. (%)	9 (18.0)	519 (13.2)
History of cardiac disorders, no. (%)†	12 (24.0)	337 (8.6)
Abnormal blood pressure, no. (%)‡	30 (60.0)	1,871 (47.5)
Current smoker, no. (%)	13 (26.0)	702 (17.8)
Concomitant medications		
Oral steroids, no. (%)	31 (62.0)	2,276 (57.8)
Statins, no. (%)	8 (16.0)	348 (8.8)
NSAIDs, no. (%)	32 (64.0)	2,832 (72.0)
Methotrexate, no. (%)	35 (70.0)	3,130 (79.5)
Methotrexate dose, mg	10.9 ± 8.1	12.0 ± 8.2
Disease status		
Duration of RA, years	9.5 ± 6.8	9.3 ± 8.5
Rheumatoid factor positive, no. (%)	38 (76.0)	3,050 (77.5)
DAS28	6.8 ± 1.4	6.4 ± 1.3
Tender joint count	17.8 ± 9.0	14.9 ± 7.8
Swollen joint count	14.4 ± 6.9	11.8 ± 6.5
Patient's global assessment, 0–100-mm VAS	65.6 ± 25.5	60.5 ± 24.7
DAS28 remission, no. (%)§	1 (2.0)	43 (1.1)
Laboratory values		
Total cholesterol, mg/dl (mmoles/liter)	204.9 ± 38.7 (5.33)	197.2 ± 42.5 (5.07)
Total cholesterol:HDL cholesterol	4.1 ± 1.4	3.7 ± 1.1
HDL cholesterol, mg/dl (mmoles/liter)	54.1 ± 15.5 (1.42)	58.0 ± 15.5 (1.47)
LDL cholesterol, mg/dl (mmoles/liter)	123.7 ± 38.7 (3.18)	116.0 ± 34.8 (2.95)
Triglycerides, mg/dl (mmoles/liter)	141.7 ± 62.0 (1.60)	124.0 ± 70.9 (1.43)
Apolipoprotein A-I, gm/liter	1.5 ± 0.3	1.5 ± 0.3
Apolipoprotein B, gm/liter	1.2 ± 0.3	1.1 ± 0.3
Apolipoprotein B: apolipoprotein A-I	0.8 ± 0.2	0.7 ± 0.3
Lp(a), mg/dl	31.0 ± 31.3	33.8 ± 33.5
C3, gm/liter	1.4 ± 0.3	1.4 ± 0.3
C4, gm/liter	0.3 ± 0.1	0.3 ± 0.1
C-reactive protein, mg/dl	2.3 ± 2.6	2.4 ± 2.9
Erythrocyte sedimentation rate, mm/hour	52.0 ± 27.1	46.1 ± 26.8
Interleukin-6, pg/ml	37.5 ± 44.8	42.3 ± 61.6
Interleukin-6 receptor, ng/ml	52.1 ± 95.4	45.6 ± 56.6
Serum amyloid A, μg/ml	54.2 ± 77.2	61.5 ± 83.5
Albumin, gm/liter	37.1 ± 3.6	38.1 ± 3.8
Haptoglobin, gm/liter	2.3 ± 0.8	2.1 ± 0.9
Absolute neutrophil count, 10^6/liter	6.0 ± 2.0	5.8 ± 2.4
Platelet count, 10^9/liter	32.6 ± 9.2	33.3 ± 10.0

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; MACE = major adverse cardiovascular event; CHD = coronary heart disease; NSAIDs = nonsteroidal antiinflammatory drugs; VAS = visual analog scale; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† Defined as including any of the following Medical Dictionary for Regulatory Activities–coded terms: angina pectoris, arrhythmia, atrial flutter, atrial fibrillation, first-degree atrioventricular block, left bundle branch block, cardiac failure, cardiac failure congestive, cardiac valve disease, cardiomegaly, cardiomyopathy, coronary artery disease, hypertensive cardiomyopathy, left ventricular hypertrophy, mitral valve incompetence, mitral valve prolapse, myocardial infarction, palpitations, sinus bradycardia, sinus tachycardia, tachycardia, tachycardia paroxysmal, tricuspid valve incompetence, and ventricular extrasystole.
‡ Defined as systolic pressure >150 mm Hg or diastolic pressure >90 mm Hg.
§ Defined as a Disease Activity Score in 28 joints (DAS28) of <2.6.

Baseline predictors of MACE. Univariate analysis demonstrated a statistically significantly increased risk of MACE in patients with a history of cardiac disorders, as reported by the investigators in these clinical trials (HR 3.63, 95% CI 1.90–6.95, $P = 0.0001$). Other statistically significant baseline predictors of MACE during TCZ treatment were older age, statin use (although use of statins was low in patients with [16%] and those without [9%] MACE) (Table 1), higher TJCs and SJCs, a higher DAS28, a higher total cholesterol:

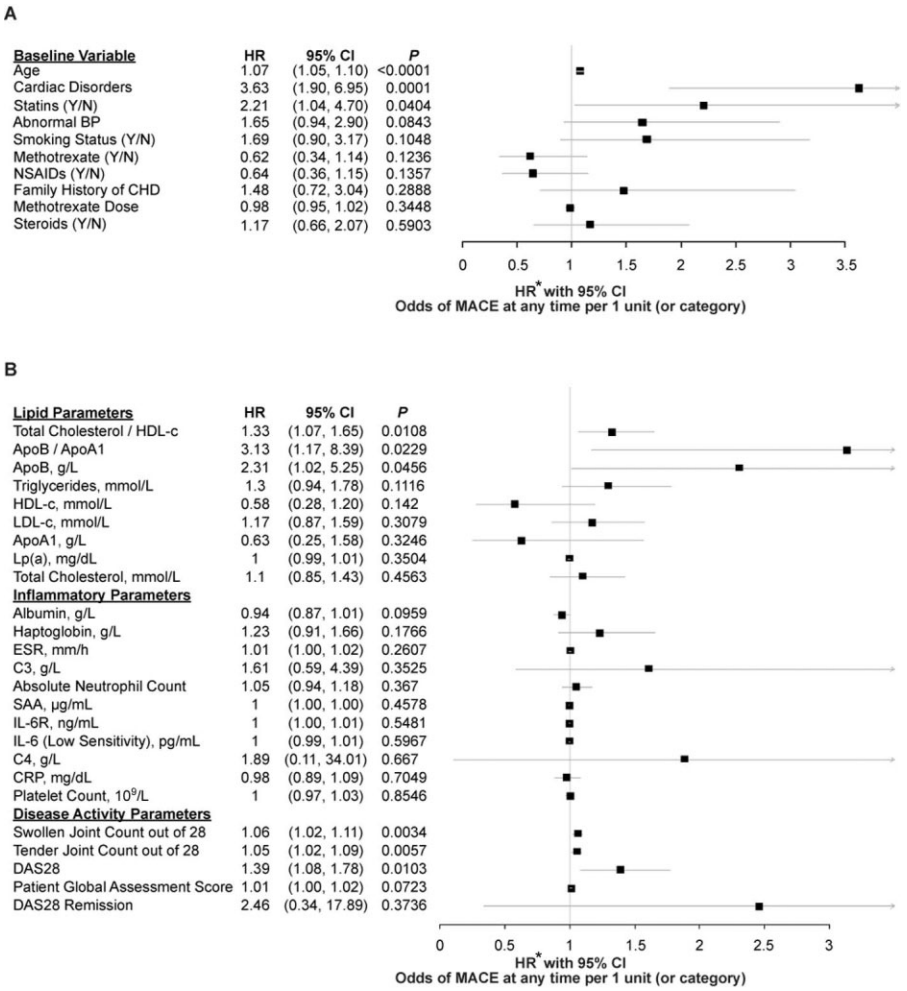

Figure 2. Univariate analysis of associations between baseline variables (demographic characteristics and medications) (**A**) and laboratory and disease parameters (**B**) and the occurrence of major adverse cardiovascular events (MACE) during tocilizumab treatment. An abnormal blood pressure (BP) was defined as systolic pressure >150 mm Hg or diastolic pressure >90 mm Hg. HR = hazard ratio; 95% CI = 95% confidence interval; NSAIDs = nonsteroidal antiinflammatory drugs; CHD = coronary heart disease; HDL-c = high-density lipoprotein cholesterol; Apo B = apolipoprotein B; LDL-c = low-density lipoprotein cholesterol; ESR = erythrocyte sedimentation rate; SAA = serum amyloid A; IL-6R = interleukin-6 receptor; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints. * = For each variable listed, a Cox regression model was fit, with the listed variables at baseline (**A** and **B**) and age (**A**) as predictors. For example, for patients of the same age, each additional swollen joint (of 28 evaluated) is associated with ~6% higher risk of MACE.

HDL cholesterol ratio and higher apolipoprotein B (Apo B) levels, and a higher Apo B:Apo A-I ratio (Figure 2). Interestingly, IL-6 and IL-6R levels at baseline were not predictive of future MACE (HR 1.00 and HR 1.00, respectively; 95% CI 0.99–1.01 and 95% CI 1.00–1.01, respectively [$P > 0.05$]). In multivariable models, older age, a history of cardiac disorders, a higher baseline DAS28, and a higher total cholesterol: HDL cholesterol ratio were independently associated with MACE during TCZ treatment (Figure 3). Complementing the associations observed at baseline, Cox proportional hazards models using single predictors observed at week 24 and adjusting for age indicated that a higher DAS28, a larger area under the curve (AUC) of the DAS28, and higher TJCs and SJCs at week 24 were statistically significant predictors of future MACE (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38920/abstract).

Changes in predictors of MACE between baseline and week 24. Greater reductions in the DAS28, SJC, and TJC from baseline to week 24 were inversely

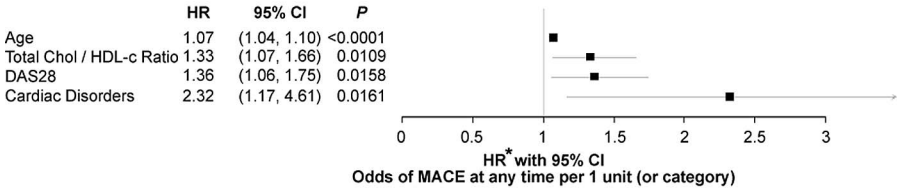

Figure 3. Multivariable analysis of the associations between baseline factors and the occurrence of MACE during tocilizumab treatment. ∗ = Multivariable Cox regression model. The set of predictors shown was determined through stepwise variable selection, with best score, forward selection, and backward selection to verify robustness. See Figure 2 for definitions.

associated with MACE, after adjusting for baseline variable levels (Figure 4). In contrast, a reduction in the ESR, changes in IL-6R levels, and changes in lipid levels between baseline and 24 weeks were not statistically significantly associated with future MACE in patients treated with TCZ (Figure 4). Mean ± SD increases in lipid levels from baseline to week 24 were of a similar magnitude in patients with MACE and those without MACE: for LDL, 0.57 ± 0.857 and 0.48 ± 0.770 mmoles/liter, respectively; for HDL, 0.06 ± 0.290 and 0.10 ± 0.303 mmoles/liter, respectively; for triglycerides, 0.39 ± 0.557 and 0.27 ± 0.809 mmoles/liter, respectively; for total cholesterol, 0.78 ± 0.970 and 0.68 ± 0.919 mmoles/liter, respectively.

DISCUSSION

To our knowledge, this study is the first to evaluate the relationship between RA disease activity, inflammation, and lipid parameters and the risk of CV events in patients with RA treated with the anti–IL-6 monoclonal antibody TCZ. Because IL-6 is a key driver of inflammation in RA, and because the rates of CVD are higher in patients with RA compared with individuals without RA, we used this population to explore the complex relationships between traditional (lipid) and RA-specific parameters and CV risk.

In the current post hoc analyses of data for patients with moderate to severe RA receiving TCZ, in which 50 independently adjudicated MACE cases were identified, we observed that a history of cardiac disorders, age at baseline, the baseline atherogenic index (ratio of total cholesterol to HDL cholesterol), and baseline RA disease activity (as assessed using the DAS28) were independently associated with MACE. This is consistent with current European League Against Rheumatism (EULAR) guidelines suggesting that the

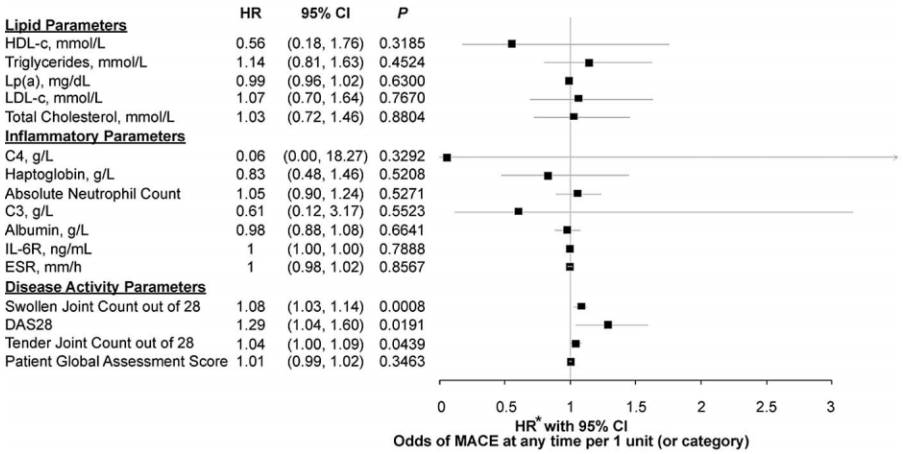

Figure 4. Age-adjusted and baseline parameter–adjusted association of changes from baseline to week 24 in lipid levels, inflammation parameters, and RA disease activity measures with future MACE. ∗ = For each variable listed, a Cox regression model was fit, with change in the variable at week 24, the variable at baseline, and age at baseline as predictors. The HR corresponds to increased risk of MACE per 1-unit increase in the parameter. For example, for patients who were the same age, started treatment with the same number of swollen joints at baseline, and were treated for 24 weeks, each additional swollen joint (of 28 evaluated) is associated with an 8% higher estimated risk of future MACE. See Figure 2 for definitions.

atherogenic index is the most stable marker of lipid-associated CV risk in RA (29).

Greater reductions in RA disease activity during TCZ therapy were associated with a statistically significantly lower risk of MACE, whereas less-robust therapeutic responses (as assessed by increases in the DAS28, SJC, and TJC from baseline to week 24) were associated with a higher risk (HR >1). As at baseline, after 24 weeks of treatment, a future risk of MACE was broadly linked to higher levels of disease activity as assessed using the DAS28, the AUC of the DAS28 (a reflection of disease burden over time), TJCs and SJCs, and a less robust therapeutic response. Inverse associations between change in disease activity measures and MACE are consistent with findings from an earlier study of a registry of patients with RA treated with anti-TNFα therapy whose risk of MI was lower by more than half if their disease responded to therapy (i.e., achievement of a good or moderate response according to the EULAR criteria) compared with nonresponders (11). Several observational studies showed that use of nonbiologic DMARDs was associated with a lower risk of MI events in patients with RA (10,11,30). A direct association regarding the long-term effect of TCZ treatment on CVD cannot be determined, given that the time during placebo treatment was limited in these trials; therefore, no robust comparison of MACE risk in placebo-treated patients is possible.

In the present analysis, baseline and week 24 levels of systemic markers of inflammation (ESR and C-reactive protein [CRP]), changes in the IL-6R level and the ESR, and changes in lipid levels over 24 weeks of TCZ treatment were not statistically significantly associated with future development of MACE. The lack of association between the ESR and the CRP level and future development of MACE may be explained by the fact that TCZ is a potent modifier of acute-phase reactants and, therefore, is a poor differentiator between patients with and those without MACE with regard to TCZ treatment (20,31). Changes in circulating levels of IL-6 were not evaluated, because TCZ treatment blocks IL-6R, resulting in elevated IL-6 levels in most treated patients.

In the trials analyzed, increases in lipid parameters were observed soon after the initiation of TCZ; mean total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels rose by 16%, 19%, 7%, and 26%, respectively, from baseline to week 6 and remained stable thereafter. Of note, rates of CV events did not appear to increase over the duration of these trials and their long-term extensions, and the CV event rates seen were consistent with those reported in the general population of patients with RA (32).

One possible explanation for the lack of an observed association between increased risk of CV events and elevated lipid levels in RA patients treated with TCZ is that inflammation, including that mediated by IL-6, can often lead to reduced lipid levels by mechanisms that are not yet fully understood. Such mechanisms may include increased peripheral catabolism (e.g., via decreases in catalytically inactive lipoprotein lipase) (33) and up-regulation of scavenger receptors leading to increased partitioning to tissue (34–36). As such, the lipid level increases observed in association with TCZ treatment may in part represent a predictable response to the suppression of inflammation. Further evidence indicating the complexity of the relationship between lipid levels and CV risk in patients with inflammatory diseases is illustrated by a cohort study in which patients with RA who had very low total cholesterol and LDL cholesterol levels were at increased risk of CVD (7). Longer-term prospective studies are needed to confirm this paradoxical observation. With regard to lipid-lowering agents, particularly statins, a low level of use was observed in this population. The association between statin use at baseline and increased risk of MACE in the univariate analysis was likely due to confounding by indication rather than to statin use itself. Indeed, some data suggest that statins may decrease the incidence of CV events in patients with RA (37), and a recent report underscores the notion that statins are likely grossly underused in the RA population (38).

The current study has several limitations. First, this post hoc exploratory analysis of safety events was conducted to investigate possible associations with patient characteristics, baseline laboratory values and disease activity parameters, and clinical response characteristics. The results were not adjusted for multiplicity testing, and the study was not specifically powered to evaluate the risk of MACE; thus, these analyses should be interpreted as hypothesis-generating. The number of MACE events (n = 50) was modest in the population analyzed (3.4/1,000 patient-years); however, this event rate is broadly similar to that observed in the British Biologics Registry (5.3/1,000 patient-years). We included all potential MACE cases based on serious adverse event reporting and then verified MACE using blinded adjudication by an independent cardiologist. Therefore, it is unlikely that MACE cases were missed.

In terms of statistical power to evaluate the association between a continuous predictor and the risk of future development of MACE, use of at least 5–10

events per predictive variable in the model is recommended to avoid bias in the estimation of regression coefficients (39,40). Nonetheless, a Type II error (i.e., failure to detect an association when it is present but potentially small) is possible. Thus, there were sufficient events for this exploratory endeavor using primarily simple models to evaluate potential risk factors, but they should be interpreted cautiously. Second, treatment was discontinued in 31% of patients during the studies. MACE cases that occurred up to 6 months after the discontinuation of TCZ were included in the analyses; beyond that point, the incidence of MACE is unclear. As such, the analyses might have been affected by informative censoring (i.e., the risk of MACE among patients who withdrew might be different from that among patients who remained in the studies). Furthermore, additional time-varying confounders, including hypertension, use of statins, and use of antiplatelet medications and glucocorticoids, were not evaluated. Finally, conclusions regarding the risk of MACE beyond the period of observation in this study (mean 3.6 years) cannot be made.

In conclusion, our data suggest that measures of disease activity may be independently related to the risk of CVD in patients with RA; in addition, an elevated atherogenic index at baseline (pretreatment) may also be independently associated with this risk. However, and of more importance to clinical practice, the current analysis suggests that changes in measures of RA disease activity, but not necessarily changes in lipid levels, are associated with incident MACE in TCZ-treated patients.

ACKNOWLEDGMENTS

We thank Jenny Devenport, PhD (Genentech), for support with the statistical analyses and Priscilla Hsue, MD (San Francisco General Hospital), for completing adjudication of the MACE cases. We also thank Mark English, PhD, Santo D'Angelo, PhD, and Meryl Mandle, who provided third-party writing assistance funded by F. Hoffmann-La Roche Ltd.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Klearman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Rao, Pavlov, Klearman, Musselman, Bathon, Sattar, Lee.

Acquisition of data. Rao, Musselman.

Analysis and interpretation of data. Rao, Pavlov, Klearman, Giles, Bathon, Sattar, Lee.

ROLE OF THE STUDY SPONSOR

F. Hoffmann-La Roche Ltd. funded the study and was responsible for the study design in collaboration with the authors. The sponsor collected, analyzed, and interpreted the data, with the authors contributing to data interpretation and the drafting/revising of the manuscript. The authors attest to the accuracy and completeness of the reported data and had final responsibility for the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by F. Hoffmann-La Roche Ltd.

ADDITIONAL DISCLOSURES

Authors Klearman and Musselman are employees of Genentech. Author Lee was an employee of Roche during the time when the study was conducted.

REFERENCES

1. Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006;65:1608–12.
2. Symmons DP, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol 2011;7:399–408.
3. Gonzalez A, Maradit Kremers H, Crowson CS, Ballman KV, Roger VL, Jacobsen SJ, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis 2008;67:64–9.
4. Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson W, Symmons D, et al. Association of the HLA–DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum 2008;58:359–69.
5. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
6. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722–32.
7. Myasoedova E, Crowson CS, Maradit Kremers H, Roger VL, Fitz-Gibbon PD, Therneau TM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70:482–7.
8. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Jacobsen SJ, Roger VL, et al. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:76–80.
9. Wolfe F, Michaud K. The risk of myocardial infarction and pharmacologic and nonpharmacologic myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case–control analysis. Arthritis Rheum 2008;58:2612–21.
10. Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55:531–6.
11. Dixon WG, Watson KD, Lunt M, Hyrich KL, British Society for Rheumatology Biologics Register Control Centre Consortium, Silman AJ, Symmons DP, on behalf of the British Society for Rheumatology Biologics Register. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti–tumor necrosis factor α therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2007;56:2905–12.

12. Lee JK, Bettencourt R, Brenner D, Le TA, Barrett-Connor E, Loomba R. Association between serum interleukin-6 concentrations and mortality in older adults: the Rancho Bernardo Study. PLoS One 2012;7:e34218.
13. Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, Angleman SB, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. PLoS Med 2008;5:e78.
14. 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.
15. Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN, et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet 2012;379:1205–13.
16. RoACTEMRA 20 mg/ml concentrate for solution for infusion [summary of product characteristics]. Welwyn Garden City (UK): Roche Registration Ltd; 2012.
17. Actemra (tocilizumab) injection for intravenous infusion [prescribing information]. South San Francisco (CA): Genentech, Inc; 2012.
18. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008;371:987–97.
19. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67:1516–23.
20. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the Tocilizumab in Combination With Traditional Disease-Modifying Antirheumatic Drug Therapy study. Arthritis Rheum 2008;58:2968–80.
21. Kremer JM, Blanco R, Brzosko S, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum 2011;63:609–21.
22. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, 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.
23. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19:12–9.
24. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Klearman M, et al. Tocilizumab monotherapy is superior to adalimumab monotherapy in reducing disease activity in patients with rheumatoid arthritis: 24-week data from the phase 4 ADACTA trial. Ann Rheum Dis 2012;71 Suppl 3:iii152.
25. Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis 2009;68:460–9.
26. Genovese MC, Rubbert-Roth A, Smolen JS, Kremer J, Khraishi M, Gomez-Reino J, et al. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. J Rheumatol 2013;40:768–80.
27. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
28. Furnival GM, Wilson RW Jr. Regressions by leaps and bounds. Technometrics 1974;16:499–511.
29. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325–31.
30. Naranjo A, Sokka T, Descalzo MA, Calvo-Alen J, Horslev-Petersen K, Luukkainen RK, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10:R30.
31. Mihara M, Kasutani K, Okazaki M, Nakamura A, Kawai S, Sugimoto M, et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int Immunopharmacol 2005;5:1731–40.
32. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther 2011;13:R14.
33. Wallberg-Jonsson S, Dahlen G, Johnson O, Olivecrona G, Rantapaa-Dahlqvist S. Lipoprotein lipase in relation to inflammatory activity in rheumatoid arthritis. J Intern Med 1996;240:373–80.
34. Gierens H, Nauck M, Roth M, Schinker R, Schurmann C, Scharnagl H, et al. Interleukin-6 stimulates LDL receptor gene expression via activation of sterol-responsive and Sp1 binding elements. Arterioscler Thromb Vasc Biol 2000;20:1777–83.
35. Hashizume M, Yoshida H, Koike N, Suzuki M, Mihara M. Overproduced interleukin 6 decreases blood lipid levels via up-regulation of very-low-density lipoprotein receptor. Ann Rheum Dis 2010;69:741–6.
36. Hashizume M, Mihara M. Atherogenic effects of TNF-α and IL-6 via up-regulation of scavenger receptors. Cytokine 2012;58:424–30.
37. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
38. Toms TE, Panoulas VF, Douglas KM, Griffiths H, Sattar N, Smith JP, et al. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? Ann Rheum Dis 2010;69:683–8.
39. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165:710–8.
40. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503–10.