Risk Factors for Major Adverse Cardiovascular Events During Tocilizumab Therapy

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Disclosures

- Vijay U. Rao: Genentech[1]
- Andrey Pavlov: Roche[2]
- Micki Klearman: Genentech[3]
- Dave Musselman: Roche[3]
- Jon Giles: Roche[4,5]
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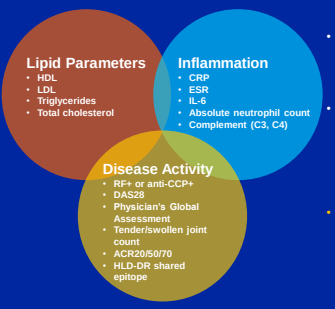
1 Research fellow; 2 Consulting fees; 3 Employee; 4 Research grant; 5 Speakers bureau; 6 Former employee.

Key References: EBM

Clinical Data Published in a Scientific Journal:

- Gonzalez A, Maradit Kremers H, 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;67:64-69.
- Dixon WG, Watson KD, Lunt M, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum*. 2007;56:2905-2912.
- Myasoedova E, Crowson CS, Kremers HM, 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;70:482-487.

Major Adverse Cardiovascular Events (MACE): Risk Factors in Patients With Rheumatoid Arthritis



- Approximately 50% of all deaths observed in RA patients are attributed to cardiovascular disease[1]
- Several studies have suggested that the increased incidence of CV events in patients with RA is not fully explained by traditional CV risk factors (DM, HTN, smoking) alone[2,3]
- The relative contributions of traditional CV risk factors, inflammation, and RA disease activity to the risk for MACE are not fully defined

1. Gabriel S. *Am J Med.* 2008;121(suppl 1):S9-S14; 2. Gonzalez A et al. *Ann Rheum Dis.* 2008;67;64-69; 3. Farragher TM et al. *Arthritis Rheum.* 2008;58:359-369.

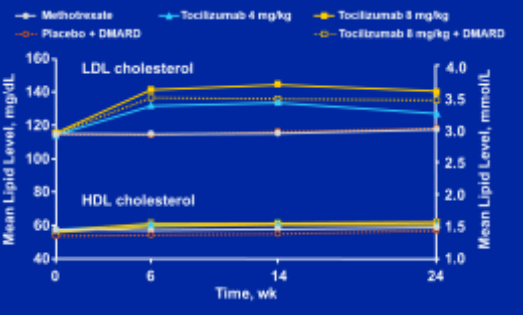
Impact of DMARDs and Biologic Therapy on Risk for MI

- DMARD use is associated with a modest reduction in MI events[1]
- Inconsistent results have been observed for effects on event rates with anti-TNF use, but a clear reduction in MI rate has been observed for anti-TNF responders[2-4]

Data Source	Patient-Years (Population)	Myocardial Infarction/100 Patient-Years (95% CI)
TCZ phase 3 Safety update July 2011:	14,994 (4009 patients)	0.25 (0.18, 0.35)

1. Suissa S et al. *Arthritis Rheum.* 2006;55:531-536; 2. Dixon WG et al. *Arthritis Rheum.* 2007;56:2905-2912; 3. Naranjo A et al. *Arthritis Res Ther.* 2008;10:R30; 4. Dixon WG et al. *Arthritis Rheum.* 2007;56:2905-2912.

Tocilizumab: Time Course of Lipid Changes Controlled 6-Month Studies

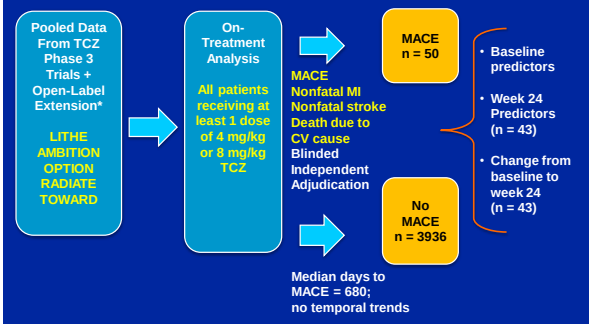


Standard deviations were approximately 25%-30% of LDL and HDL values.
Genovese M et al. *ACR* 2008. Poster 987.

Key Questions

1. What baseline risk factors (demographic, RA disease activity, lipid, or inflammation) are associated with MACE on TCZ therapy?
2. Do changes in lipid or inflammation parameters, or RA-specific disease activity measures, alter the risk for MACE on TCZ therapy?

Methods: Post Hoc, Retrospective, On-Treatment MACE Analysis



*Men and women older than age 18 and weighing ≤150 kg, with moderate to severe active RA of ≥ 6 months' duration, who have an inadequate clinical response to methotrexate. Mean TCZ exposure: 3.07 years

Statistical Methods

Objective: Evaluate the association of various patient characteristics and study assessments with time to future MACE on TCZ treatment

- Univariate Cox proportional hazards modeling
  - Demographic characteristics, medical history, and baseline disease activity
- Cox proportional hazards modeling
  - Disease and laboratory characteristics at week 24 and change from baseline to week 24
- Multivariate Cox proportional hazards modeling
  - Medical history and baseline characteristics that jointly predict time to MACE.

- Hazard ratios (HR) are reported along with 95% confidence intervals and corresponding p-values for the test of no association (HR=1). Adjustment of HR for age or other baseline variables as noted.

Measured Predictors

Demographic/History

Age
Cardiac disorders
Abnormal BP
Family history heart disease
MTX dose
MTX (Y/N)
NSAIDs (Y/N)
Smoking status (Y/N)
Statins (Y/N)
Steroids (Y/N)
BMI
Gender

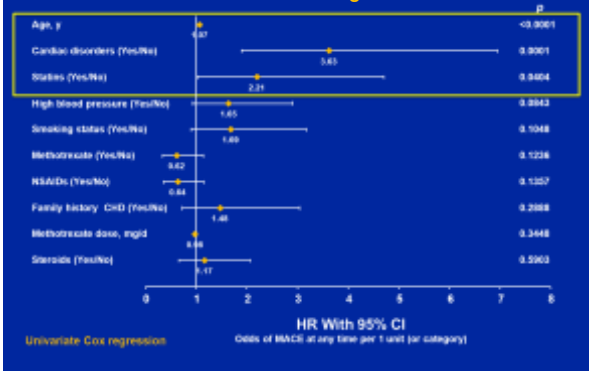
RA Disease (BL, Wk 24, Δ from BL)

Swollen joint count out of 28
Tender joint count out of 28
DAS28
Patient Global Assessment Score
DAS28 remission
EULAR response (Good/not)
AUC of DAS28
ACR 20/50/70

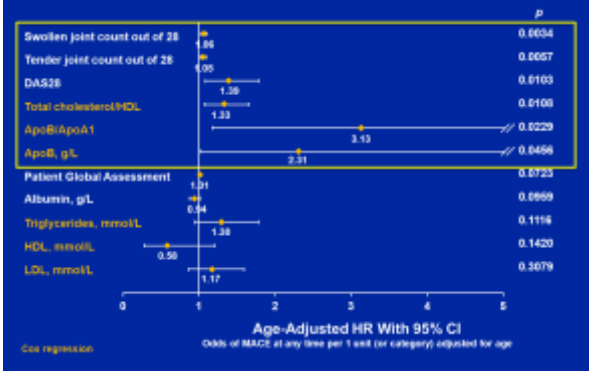
Laboratory (BL, Wk 24, Δ from BL)

Absolute neutrophil count
Albumin
ApoA1
ApoB
ApoB/ApoA1
C3
C4
CRP
ESR
Haptoglobin
HDL
IL-6 (low sensitivity)
IL-6R
LDL
Lipoprotein (a)
Platelet count
SAA
Total cholesterol
Total cholesterol/HDL
Triglycerides

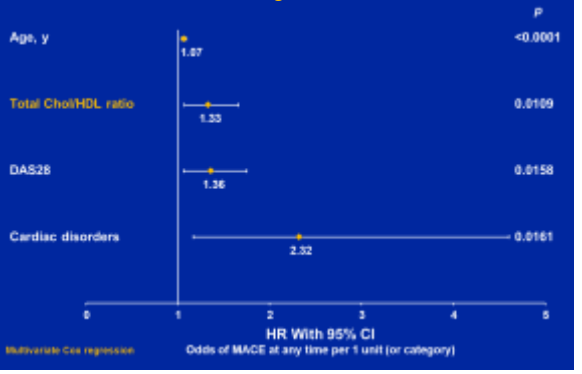
Age, History of Cardiac Disorders, and Statin Use Are Associated With MACE During TCZ Treatment



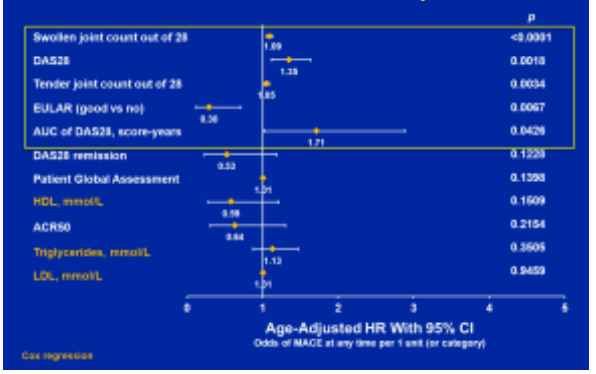
Baseline Disease Measures and Laboratory Parameters Evaluated for Associations With MACE



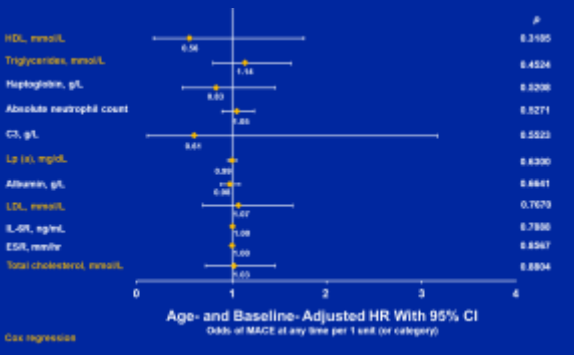
Age, Atherogenic Index, Disease Activity, and History of Cardiac Disorders Are Multivariate Predictors of MACE During TCZ Treatment



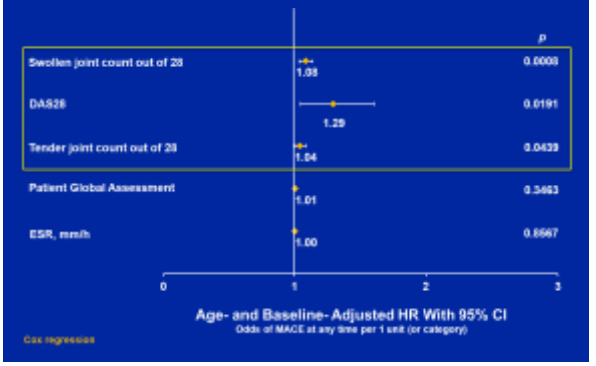
Post-TCZ Treatment Predictors (Week 24) of Future MACE (Adjusted for Age) Are Limited to Measures of Disease Activity



Changes From Baseline to Week 24 in Lipid and Inflammation Parameters Evaluated for Associations With MACE During TCZ Treatment



Increases or Smaller Reductions from Baseline to Week 24 in Measures of Disease Activity are Associated With MACE During TCZ Treatment



Summary:
Factors Associated With MACE in Tocilizumab Clinical Trials

Baseline	After 24 Weeks of Tocilizumab Treatment	Change From Baseline
Traditional Factors • Baseline age • Cardiac disorders • Total cholesterol/HDL • Baseline statin use • ApoB • ApoB/ApoA1 **RA- and Inflammation-Specific Factors** • Swollen and tender joint counts (28) • DAS28 score	• Swollen and tender joint counts • DAS28 • EULAR (good vs no) • AUC of DAS28, score-years	• Changes in lipid and inflammation parameters from baseline to week 24 were NOT associated with post-week 24 MACE • Reductions in RA disease activity from baseline to week 24 were associated with fewer MACE

Higher values are associated with increased risk for MACE, except for response (change from baseline in disease activity and joint counts) where improvement or achievement of "good" EULAR response is associated with reduced risk for MACE.

Limitations

- Small number of MACE: though one of the largest on-treatment analyses conducted to date
- Treatment withdrawal: treatment discontinuation in 31% of patients during the studies (informative censoring?)
- Additional time-varying confounders: hypertension, antiplatelet medications, glucocorticoids, and unmeasured factors
- No comparator (pbo): whether risk for MACE increased with TCZ exposure not addressed
- No causality established: predictors/models consistent with the observed events identified

Conclusions

- As has been seen with other biologics in RA patients, greater reductions in disease activity/burden on TCZ was associated with a reduction in MACE
- RA patients receiving tocilizumab should be aggressively screened and treated for traditional CV risk factors (e.g., lipids)
- TCZ induced lipid changes during the first six months of therapy do not appear to confer increased risk of MACE
- Assessment of lipid parameters should be performed soon after initiation of treatment and patients should be managed according to accepted guidelines

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Authors

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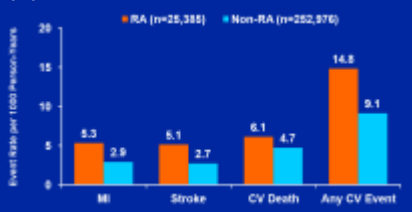
Backup

CV Risk Factors in RA Patients

Gonzalez A et al. *Ann Rheum Dis.* 2008;67;64-69.
Farragher TM et al. *Arthritis Rheum.* 2008;58:359-369.

Background

- Approximately 50% of RA patient deaths are attributed to cardiovascular causes
- Morbidity and mortality studies show that the incidence of CV disease is about 1.5- to 3-fold greater in RA patients than in the general population



MI = Myocardial infarction; CV = cardiovascular.
Solomon DH et al. *Ann Rheum Dis.* 2006;65:1608-1612.

Rate of Cardiovascular Events in Tocilizumab Phase 3 Program

Cardiovascular Events	All-Exposed Population N=4009 14,994 PY exposure
	Rate/100 PY (number of events) [95% CI]
MI	0.25 (38) [0.18, 0.35]
Stroke (ischemic and hemorrhagic)	0.31 (47) [0.23, 0.42]

Safety Update July 2011.

On-Treatment Analysis of MACE With Tocilizumab

Population	• Pooled data from 5 TCZ phase 3 trials and open-label extensions (AMBITION, OPTION, TOWARD, LITHE, and RADIATE) • On treatment analysis — patients who received ≥1 dose of TCZ (4 or 8 mg/kg) • Occurrence of MACE after TCZ exposure
Design	• Post hoc, retrospective analysis • All adverse events in database and classified as MI, stroke, or death due to CV cause evaluated (50 MACE) • All events adjudicated by a blinded, independent third party
Sample	• Without MACE, n = 3936 • With adjudicated MACE, n = 50 • For 50 adjudicated MACE to date: Days from first TCZ exposure to MACE: minimum 29, maximum 1792, median 680 Rates appear constant throughout study period

Statistical Methods

- Cox proportional hazards models were fitted to evaluate the association of demographics and baseline disease characteristics with time to MACE during TCZ treatment
- Cox proportional hazards models were fitted to evaluate the association of disease and laboratory characteristics at week 24 with MACE occurring after 24 weeks of exposure to TCZ after adjusting for age
- Multivariate Cox proportional hazards models were examined to see which medical history characteristics jointly predicted time to MACE. Variable selection proceeded using multiple algorithms
- Robustness of multivariate modeling was evaluated by refitting the model with a new data cut (8 additional cases) and, separately, 5 additional "probable" cases

Sensitivity Analysis: Cox Regression to Predict MACE From Age and Medical History