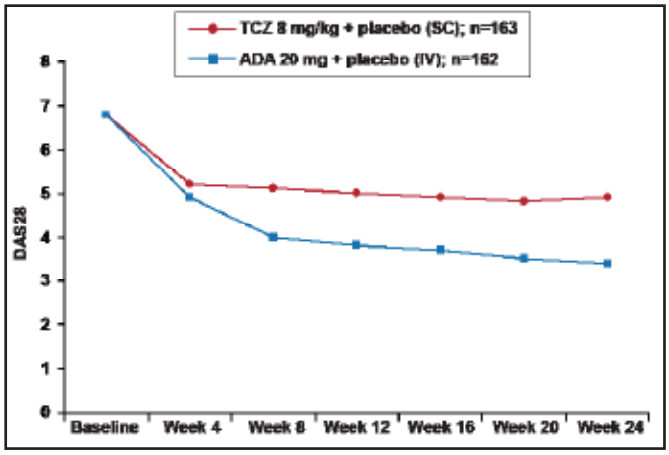
tocilizumab 8 mg/kg every 4 weeks plus subcutaneous placebo (n=163) or adalimumab 40 mg subcutaneously every 2 weeks plus intravenous placebo (n=163). Patients who did not achieve at least a 20% improvement from baseline in swollen and tender joint count at Week 16 or later could escape to weekly subcutaneous injections of adalimumab/placebo.

At Week 24, the change from baseline in DAS28 was -3.3 for the tocilizumab group versus -1.8 for subjects who received adalimumab (difference, 1.5; 95% CI for difference, -1.8 to -1.1; p<0.0001). Differences were observed, beginning at Week 8 (Figure 1). Significantly (p<0.0001) more subjects in the tocilizumab group also achieved the secondary endpoints of remission and low disease activity compared with those who received adalimumab (39.9% versus 10.5% and 51.5% versus 19.8%, respectively). ACR20/50/70 responses were also significantly (p<0.01) better among the tocilizumab subjects (65.0%, 47.2%, 32.5%) compared with subjects who received adalimumab (49.4%, 27.8%, 17.9%). In the *post hoc* analysis for CDAI response, 47.9% of tocilizumab versus 29.0% of adalimumab subjects (p=0.0003) were considered to be in remission or have low disease activity (CDAI score ≥0 to ≤10).

Figure 1. DAS28: Mean (±SE) Over Time.



TJC=tender joint count; SJC=swollen joint count; TCZ=tocilizumab; ADA=adalimumab; LOCF used for TJC and SJC; ESR and Patient's Global Assessment of Disease Activity VAS; If ESR=0 then ESR=1 is substituted into the DAS28 calculation to enable a non-missing DAS28.
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The incidence of AEs was similar (82.1% in the tocilizumab arm and 82.7% in the adalimumab arm). Serious AEs and serious infections were also similar (tocilizumab: 11.7%, 3.1%; adalimumab: 9.9%, 3.1%). Changes in transaminase, low-density lipoprotein elevations, and neutrophil reductions occurred in both arms, with the proportion of patients with abnormal values higher in the tocilizumab arm. There were 2 deaths in the tocilizumab arm; 1 from sudden death that was considered to possibly be related to the study drug and 1 from illicit drug overdose that was not considered to be related.

Efficacy of Different Doses of Rituximab for the Treatment of RA: Data From the CERERRA Collaboration

Written by Toni Rizzo

The approved dose of rituximab for the treatment of rheumatoid arthritis (RA) is 1000 mg x 2, but some data have suggested similar clinical efficacy with rituximab 500 mg x 2. The objective of this analysis, presented by Katerina Chatzidionysiou, MD, Karolinska Institute, Stockholm, Sweden, was to compare the efficacy of the 2 doses, given as first or second treatment courses.

The data for this analysis were obtained from the European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis (CERERRA), which includes 10 European registries. The registries submitted anonymous datasets with demographic, efficacy, and treatment data on patients who had started rituximab therapy. Treatment and retreatment efficacy were assessed by Disease Activity Score (DAS) 28 reductions and EULAR responses after 6 months.

Information on rituximab doses was available for 2873 (88%) of 3266 patients in the registries. A total of 2625 patients (91.4%) received 1000 mg x 2 of rituximab, and 248 patients (8.6%) received 500 mg x 2. Baseline characteristics that were significantly different between the 500 mg x 2 and 1000 mg x 2 groups, respectively, were: age (55.2 vs 52.6 years; p=0.002), disease duration (13.6 vs 10.9 years; p<0.0001), number of prior biologics (0.7 vs 1.0; p <0.0001), number of prior disease-modifying antirheumatic drugs (DMARDs; 2.6 vs 2.4; p=0.04), baseline DAS28 (5.7 vs 5.9; p=0.02), concurrent DMARDs (72.6% versus 83.1%; p<0.0001), concurrent corticosteroids (65.7% vs 59.3%; p=0.03), and TNF-naïvete (42% vs 62.5%; p<0.0001).

There were no significant differences in DAS28 or Health Assessment Questionnaire (HAQ) responses between the 2 dose groups at 3 months and 6 months. The change in ΔDAS28 at 3 months was 1.3±1.3 in the 500 mg x 2 group versus 1.8±1.4 in the 1000 mg x 2 group (p=0.005, corrected for baseline difference in DAS28). The Δ HAQ at 3 months was 0.3±0.5 in the 500 mg x 2 group versus 0.5±0.6 in the 1000 mg x 2 group (p=0.02). There was no significant difference between the 2 groups in change in DAS28 or HAQ at 6 months. No significant difference was seen in EULAR response or remission rates between the 2 dose groups.

Data on 622 patients who received a second cycle with 2 rituximab infusions were available at 6±1 months. At 6 months after retreatment, the 1000 mg x 2 group versus the 500 mg x 2 group had significant improvements in

DAS28 at 12 months (p<0.0001), change in DAS28 at 12 months (p=0.001), and change in DAS28 from 6 to 12 months (p=0.015). EULAR response at 6 months after retreatment was significantly improved in the 1000 mg x 2 versus the 500 mg x 2 group (p<0.0001), but the difference in remission rates was not significant.

In this large, observational cohort, initial treatment with rituximab at 500 mg x 2 and 1000 mg x 2 led to comparable clinical outcomes. The 1000 mg x 2 dose was associated with further DAS28 reductions when given as a second treatment course.

Anti-TNF Therapy and CV Risk in RA

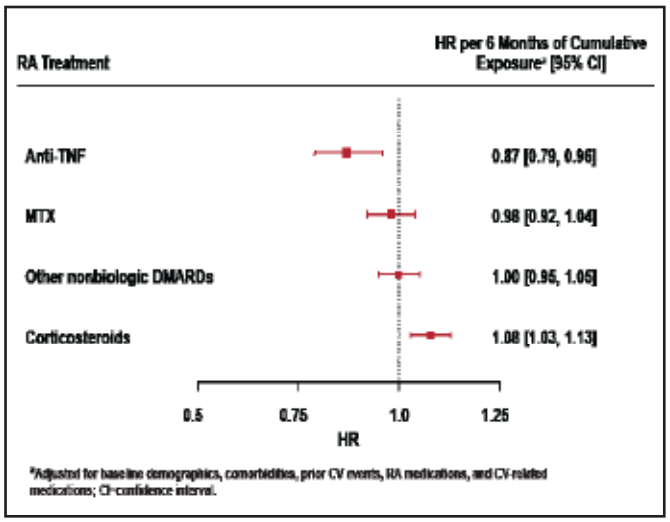
Written by Toni Rizzo

Systemic inflammation in patients with rheumatoid arthritis (RA) leads to a greater risk of cardiovascular (CV) events that are linked to tumor necrosis factor (TNF)-related atherogenesis. Anti-TNF therapies have been shown in observational studies to reduce the risk of CV events in patients with RA. The objective of this retrospective medical record review, presented by Michael T. Nurmohamed, MD, PhD, VU University Medical Center and Jan van Breemen Research Institute, Amsterdam, The Netherlands, was to compare the effect of exposure to anti-TNF treatment on the risk of CV events in patients with RA with those who were treated with methotrexate and other disease-modifying therapies.

The study population was drawn from the Thomson Reuters Market Scan Commercial Claims Database between January 1, 2003 and December 31, 2010. Selected patients were required to have at least 2 RA diagnoses and be aged ≥18 years. Patients' records were evaluated from the index date (first anti-TNF prescription fill date or random date for patients without anti-TNF prescription) to the end of health plan enrollment, end of data availability, or 6 months after discontinuation of therapy. The primary endpoint was the composite of myocardial infarction (MI), stroke, unstable angina, or congestive heart failure (CHF). The secondary endpoint was individual CV events. Cumulative exposures were calculated for anti-TNF therapy, methotrexate, other nonbiologic disease-modifying antirheumatic drugs (DMARDs), and corticosteroids.

A total of 109,462 patients were assessed; of them, 1743 patients (1.6%) had at least 1 study CV event. In the multivariate regression model, each additional 6 months of anti-TNF therapy significantly reduced the risk for any study CV event. Patients who were treated with anti-TNF therapy had a hazard ratio (HR) of 0.87 (95% CI, 0.79 to 0.96; p=0.005) for the composite CV event endpoint compared with 0.98 (95% CI, 0.92 to 1.04) in patients who were treated with methotrexate, 1.00 (95% CI, 0.95 to 1.05) in patients who were treated with other nonbiologic DMARDs, and 1.08 (95% CI, 1.03 to 1.13) in patients who were treated with corticosteroids (Figure 1). The multivariate regression model predicted that cumulative use of anti-TNF therapy would result in a 24% reduction in CV events at 1 year, 42% reduction at 2 years, and 56% reduction at 3 years compared with not using anti-TNF therapy, adjusting for background use of methotrexate or other nonbiologic DMARDs.

Figure 1. HRs for Composite CV Event by RA Treatment.



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Each additional 6 months of anti-TNF therapy was associated with CV risk reduction in patients aged ≥50 years (HR, 0.86; 95% CI, 0.77 to 0.96; p=0.007). Risk reduction in methotrexate-naïve patients (HR, 0.85; 95% CI, 0.73 to 0.98; p=0.022) was similar to that observed in the total population. The hazard ratios for individual CV events in patients who were treated with anti-TNF drugs were 0.80 (95% CI, 0.67 to 0.95) for MI; 0.99 (95% CI, 0.86 to 1.16) for stroke, 0.76 (95% CI, 0.63 to 0.91) for unstable angina, and 0.78 (95% CI, 0.67 to 0.91) for CHF.

These results build on the findings of existing studies that have shown statistically significant CV risk reduction that was associated with anti-TNF therapy in RA patients (Table 1). Limitations of this study include the retrospective design, with the potential for unobserved confounding variables. In addition, clinical variables, such as lipid levels, blood pressure, and smoking status, were not available. The analysis adjusted for CV risk factors at baseline, including prior inpatient CV events, history of comorbidities, and CV-related medications.