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

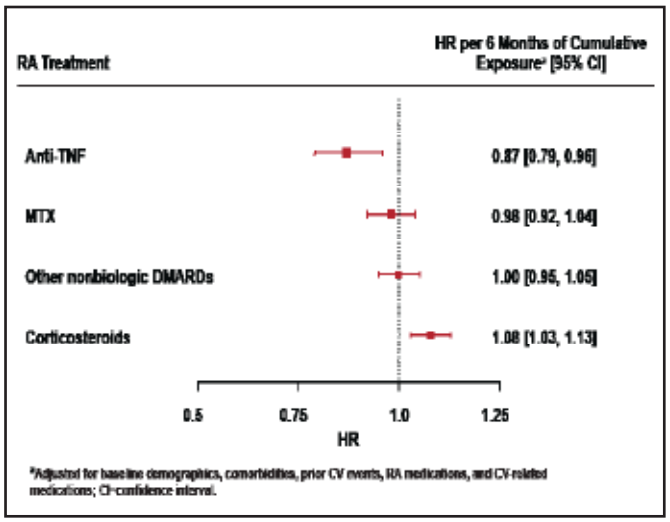
Written by Toni Rizzo

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.

Longer exposure to anti-TNF therapy was associated with a greater reduction in the risk of CV events, primarily myocardial infarction, unstable angina, and congestive heart failure. Risk reduction was also observed in older patients and in methotrexate-naïve patients. Risk reduction was not observed for cumulative exposure to methotrexate or nonbiologic DMARDs.

Table 1. Findings Support Existing Studies.

Study	Population	Exposure	Outcome Measure	Anti-TNF RR or HR
Greenberg et al.	US patients with RA in CRRNA RA registry	Anti-TNF ± MTX vs other nonbiologic DMARDs	• MI/CVA/ TIA/CV death	0.39*
Ljung et al.	Swedish Rheumatology Register	Anti-TNF vs patients with no exposure to anti-TNF	• Acute coronary syndromes	0.80
Barnabe et al.	Meta-analysis of 11 published observational studies	Anti-TNF vs nonbiologic DMARDs	• MI/CHF/ CVA • MI • CVA	0.46* 0.81* 0.69*
Narango et al.	Multinational cross-sectional cohort of consecutive outpatients with RA	Cumulative exposure to anti-TNF vs other (by year)	• MI/CVA/ angina/ coronary disease/ bypass surgery • MI • CVA	0.64* 0.42* 0.64

*Values are statistically significant at the 5% level; CRRNA=Consortium of Rheumatology Researchers of North America; RA=rheumatoid arthritis; MTX=methotrexate; MI=myocardial infarction; CVA=cerebral vascular accident; TIA=transient ischemic attack; CHF=congestive heart failure; CV=cardiovascular; DMARD=disease modifying antirheumatic drug.

12-Week Results of a Phase 2b Dose-Ranging Study of Baricitinib (LY3009104) in Combination with Traditional DMARDs in Patients with RA

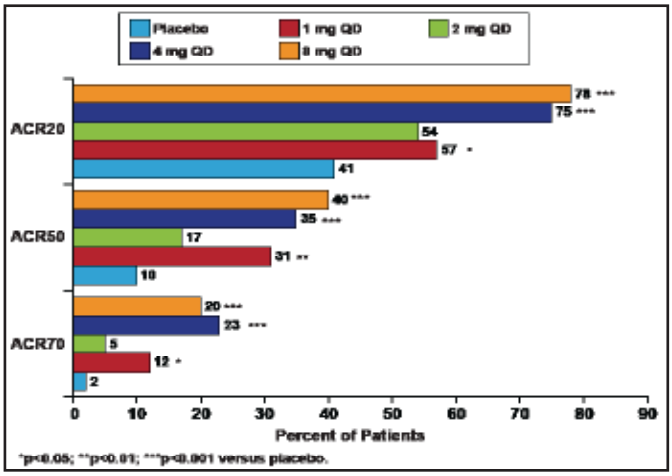
Written by Maria Vinall

Data from a Phase 2b study, presented by Edward Keystone, MD, University of Toronto, Toronto, Ontario, Canada, suggest that baricitinib, an oral JAK1/JAK2 inhibitor, is an efficacious treatment for rheumatoid arthritis (RA) when used in combination with traditional disease-modifying antirheumatic drugs (DMARDs).

JAK tyrosine kinases differentially mediate signal transduction for a variety of cytokines that are involved in inflammatory conditions. JAK1 and JAK2 particularly affect IL-6, IL-12, IL-23, INF-γ, and INF-α/β, suggesting that inhibition of JAK1 or JAK2 would lead to immunomodulation or perhaps immunosuppression. This was a double-blind, placebo-controlled, randomized study to assess the effect of 4 doses of baricitinib, a potent, reversible inhibitor of JAK1 and JAK2, in patients with RA. Eligible subjects had ≥8 swollen and ≥8 tender joints, based on the 66/68 joint count; were on a stable dose of methotrexate for at least 12 weeks or corticosteroids for 6 weeks; and had a maximum C-reactive protein (CRP) level >1.2x the upper limit of normal or an erythrocyte sedimentation rate >28 mm/hr. Subjects were randomized to placebo (n=98) or baricitinib 1, 2, 4, or 8 mg daily (~50 subjects each) in combination with methotrexate and treated for 12 weeks. The primary study endpoint was the ACR20 response at Week 12 for the combined 4- and 8-mg dose groups versus placebo. Major secondary endpoints included ACR20/50/70 and DAS28-CRP response at 12 weeks, safety and tolerability, pharmacokinetics, and patient-reported outcomes.

A total of 301 subjects (mostly women, mean disease duration of ~5.5 years) were enrolled. Subjects in this study had active disease (tender joint count 22/68; swollen joint count 16/66; mean DAS28-CRP score of 5.5; mean Health Assessment Questionnaire [HAQ] score 1.2). At 12 weeks, 76% of subjects who received either 4 or 8 mg of baricitinib achieved the primary endpoint of ACR20 response compared with 41% of placebo-treated patients ($p<0.001$). Treatment with baricitinib also led to significant ($p<0.05$) improvements in ACR20/50/70 at all doses except 2 mg (Figure 1). DAS28-CRP <2.6 response was achieved by 37% of subjects in the 4-mg group and 22% of those in the 8-mg group ($p<0.05$ vs placebo). The onset of efficacy was rapid for ACR20/50/70 and DAS28-CRP, with statistically significant differences seen after 2 weeks of therapy. Simplified Disease Activity Index and Clinical Disease Activity Index remission was achieved more frequently by patients in the 4-mg group (18% and 22%, respectively; both $p<0.05$ vs placebo). Sixty percent of subjects in the 4-mg group and 67% of those in the 8-mg group achieved the minimum clinically important difference for the HAQ-Disability Index compared with placebo (41%) at Week 12.

Figure 1. ACR Responses by Dose at 12 Weeks.



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