RA, Cardiovascular Markers Predict CV Events

BY MARY ANN MOON

FROM THE ANNALS OF RHEUMATIC DISEASES

Both markers of rheumatoid arthritis severity and traditional markers of cardiovascular risk are important and independent predictors of future CV events among patients who have RA, according to a report published in the Annals of the Rheumatic Diseases.

Clinicians therefore can target both types of markers to reduce the incidence of CV events, which are the major source of mortality in patients with RA, said Dr. Daniel H. Solomon, chief of the section of clinical sciences in the division of rheumatology, immunology, and allergy at the Brigham and Women's Hospital, Boston, and his associates.

The investigators examined the relative importance of the two types of markers in predicting CV events using a large, longitudinal cohort of RA patients: subjects enrolled in CORRONA (Consortium of Rheumatology Researchers of North America), which includes more than 17,000 patients treated by 268 academic and community rheumatologists at 103 medical centers across the United States. Enrollment began in 2002, and patients were followed through 2006.

For this analysis, 10,156 subjects were followed for a median of 22 months for the development of incident MI, stroke, or transient ischemic attack. Cases of heart failure, peripheral artery disease, and CV-related death were excluded from the study. The subjects' mean age was 59 years, and 75% were women. Median disease duration at baseline was 7 years.

There were 29 MIs and 47 strokes or TIAs during follow-up, for an event rate of about 4 per 1,000 person-years.

Six traditional markers of CV risk – hypertension, diabetes, hyperlipidemia, current tobacco use, known cardiovascular disease, and a family history of premature (at age 50 years or younger) CV events – were important predictors of CV events during follow-up. In addition, seven markers of RA severity – disease duration greater than 5 years, radiographically evident joint erosions, subcutaneous nodules, prior total joint replacement, a score of 2 or more on the modified Health Assessment Questionnaire, a score of 2.3 or more on the Clinical Disease Activity Index, and seropositivity for rheumatoid factor – were strong, independent predictors of CV risk.

Moreover, the incidence of CV events escalated as the number of either type of risk factor increased. The incidence was 0 among patients with no CV risk factors and no markers of RA severity, and it rose to 7.5 per 1,000 person-years in patients with two or more CV risk factors and three or more markers of RA severity, Dr. Solomon and his colleagues said (Ann. Rheum. Dis. 2010;69:1920-5).

In statistical models that incorporated both types of risk factors plus patient age and sex, the predictive value was comparable to that calculated using the Framingham risk score, they noted.

"These results suggest that strategies to reduce CV risk should focus on a strategy of controlling both traditional CV risk factors as well as controlling RA severity," the investigators said.

A large clinical trial statin use for primary prevention of CV events in RA patients is now under way, they added. ■

VITALS

Major Finding: Seven markers of RA severity and six markers of cardiovascular risk were important and independent predictors of MI, stroke, or TIA during 2 years of follow-up in patients with RA.

Data Source: Post hoc analysis of data on 10,156 patients with RA enrolled in CORRONA, a longitudinal cohort study involving 103 U.S. medical centers.

Disclosures: There was no specific support for this analysis. CORRONA has received general support in the last 2 years from Abbott, Amgen, BMS, Centocor, Genentech, Lilly, and Roche. Dr. Solomon receives support from the National Institutes of Health, the Agency for Healthcare Quality and Research, the Arthritis Foundation, Abbott, and Amgen.

alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI® and abatacept is not recommended (see Drug Interactions). **Use with Anakinra** Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI®, is not recommended (see Drug Interactions). **Hematologic Cytopenias** There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. Although, there were no cases of severe cytopenias seen in the SIMPONI® clinical trials, caution should be exercised when using TNF-blockers, including SIMPONI®, in patients who have significant cytopenias. **Vaccinations** Patients treated with SIMPONI® may receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection after the administration of live vaccines to patients receiving SIMPONI®. In the Phase 3 PsA study, after pneumococcal vaccination, a similar proportion of SIMPONI®-treated and placebo-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI®-treated and placebo-treated patients, the proportions of patients with response to pneumococcal vaccine were lower among patients receiving MTX compared with patients not receiving MTX. The data suggest that SIMPONI® does not suppress the humoral immune response to the pneumococcal vaccine. **ADVERSE REACTIONS** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. **Clinical Studies Experience** The safety data described below are based on 5 pooled, randomized, double-blind, controlled Phase 3 trials in patients with RA, PsA, and AS (Studies RA-1, RA-2, RA-3, PsA and AS). These 5 trials included 639 control-treated patients and 1659 SIMPONI®-treated patients including 1089 with RA, 292 with PsA, and 277 with AS. The proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI®-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI® in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%). The most serious adverse reactions were: Serious Infections; Malignancies. Upper respiratory tract infection and nasopharyngitis, were the most common adverse reactions reported in the combined Phase 3 RA, PsA and AS trials through Week 16, occurring in 7% and 6% of SIMPONI®-treated patients as compared with 6% and 5% of control-treated patients, respectively. **Infections** In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28% of SIMPONI®-treated patients compared to 25% of control-treated patients. **Liver Enzyme Elevations** There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of SIMPONI® in patients with RA, PsA, and AS through Week 16, ALT elevations ≥5 x ULN occurred in 0.2% of control-treated patients and 0.7% of SIMPONI®-treated patients, and ALT elevations ≥3 x ULN occurred in 2% of control-treated patients and 2% of SIMPONI®-treated patients. Since many of the patients in the Phase 3 trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX), the relationship between SIMPONI® and liver enzyme elevation is not clear. **Autoimmune Disorders and Autoantibodies** The use of TNF-blockers has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome. In the controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, there was no association of SIMPONI® treatment and the development of newly positive anti-dsDNA antibodies. **Injection Site Reactions** In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI® treated patients had injection site reactions compared with 2% of control-treated patients. The majority of the injection site reactions were mild and the most frequent manifestation was injection site erythema. In controlled Phase 2 and 3 trials in RA, PsA, and AS, no patients treated with SIMPONI® developed anaphylactic reactions. **Psoriasis: New-Onset and Exacerbations** Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been reported with the use of TNF-blockers, including SIMPONI. Cases of exacerbation of pre-existing psoriasis have also been reported with the use of TNF-blockers. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of SIMPONI® should be considered for severe cases and those that do not improve or that worsen despite topical treatments. **Immunogenicity** Antibodies to SIMPONI® were detected in 57 (4%) of SIMPONI®-treated patients across the Phase 3 RA, PsA and AS trials through Week 24. Similar rates were observed in each of the 3 indications. Patients who received SIMPONI® with concomitant MTX had a lower proportion of antibodies to SIMPONI® than patients who received SIMPONI® without MTX (approximately 2% versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI® in the Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as measured by a cell-based functional assay. The small number of patients positive for antibodies to SIMPONI® limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures. The data above reflect the percentage of patients whose test results were considered positive for antibodies to SIMPONI® in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SIMPONI® with the incidence of antibodies to other products may be misleading. **Other Adverse Reactions** The adverse drug reactions that occurred at a rate of at least 1% in the combined SIMPONI® groups during the controlled period of the 5 pooled Phase 3 trials through Week 16 in patients with RA, PsA, and AS are summarized below. Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low-dose corticosteroids (≤10 mg of prednisone/day or equivalent), and/or NSAIDs during the trials. The numbers (percentages) of adverse drug reactions for Placebo ± DMARDS-treated patients (n=639) and SIMPONI® ± DMARDS-treated patients (n=1659), respectively, were:

	Placebo ± **DMARDS**	SIMPONI® ± **DMARDS**
Upper respiratory tract infection	37 (6%)	120 (7%)
Nasopharyngitis	31 (5%)	91 (6%)
Alanine aminotransferase increased	18 (3%)	58 (4%)
Injection site erythema	6 (1%)	56 (3%)
Hypertension	9 (1%)	48 (3%)
Aspartate aminotransferase increased	10 (2%)	44 (3%)
Bronchitis	9 (1%)	31 (2%)
Dizziness	7 (1%)	32 (2%)
Sinusitis	7 (1%)	7 (2%)
Influenza	7 (1%)	25 (2%)
Pharyngitis	8 (1%)	22 (1%)
Rhinitis	4 (< 1%)	20 (1%)
Pyrexia	4 (< 1%)	20 (1%)
Oral herpes	2 (< 1%)	16 (1%)
Paraesthesia	2 (< 1%)	16 (1%)

Less common clinical trial adverse drug reactions Adverse drug reactions that occurred <1% during the SIMPONI clinical trials included the following events listed by system organ class: *Nervous system disorders:* central nervous system demyelinating disorders (such as multiple sclerosis), peripheral demyelinating polyneuropathy **DRUG INTERACTIONS: Methotrexate**. For the treatment of RA, SIMPONI® should be used with MTX. Since the presence or absence of concomitant MTX did not appear to influence the efficacy or safety of SIMPONI® in the treatment of PsA or AS, SIMPONI® can be used with or without MTX in the treatment of PsA and AS. **Biologic Products for RA, PsA, and/or AS** An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI® with abatacept or anakinra is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. There is insufficient information to provide recommendations regarding the concomitant use of SIMPONI® and other biologic products approved to treat RA, PsA, or AS. **Live Vaccines** Live vaccines should not be given concurrently with SIMPONI®. **Cytochrome P450 Substrates** The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI® in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. **USE IN SPECIFIC POPULATIONS: Pregnancy** Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI® in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI® should be used during pregnancy only if clearly needed. An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (360 times greater than the maximum recommended human dose-MHRD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus. A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (860 times and 310 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to 6 months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants. **Nursing Mothers** It is not known whether SIMPONI® is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SIMPONI®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations. **Pediatric Use** Safety and effectiveness of SIMPONI® in patients less than 18 years of age have not been established. **Geriatric Use** In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious infections, and AEs in SIMPONI®-treated patients ages 65 or older (N=155) compared with younger SIMPONI®-treated patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI®. **OVERDOSAGE** In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of intravenous SIMPONI® without serious adverse reactions or other significant reactions. The highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000 mg of SIMPONI®. There were no SIMPONI® overdoses in the clinical studies. **PATIENT COUNSELING INFORMATION Patient Counseling** Patients should be advised of the potential benefits and risks of SIMPONI®. Physicians should instruct their patients to read the Medication Guide before starting SIMPONI® therapy and to read it each time the prescription is renewed. **Infections** Inform patients that SIMPONI® may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation. **Malignancies** Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMPONI®. **Allergic Reactions** Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringe in the prefilled SmartJect® autoinjector contains dry natural rubber (a derivative of latex). **Other Medical Conditions** Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cytopenias, or psoriasis.

References: 1. SEER [database online]. U.S. Population Data—1969-2004. Bethesda, MD; National Cancer Institute. Release date: January 3, 2007. Available at: http://www.seer.cancer.gov/popdata.

©2010 Centocor Ortho Biotech Inc. License No. 1821
Horsham, PA 19044, US 1-800-457-6399 July 2010 25SMRA10016